AD_____

Contract Number DAMD17-97-C-7034

TITLE: Extracorporeal Life Support in Military Casualties

PRINCIPAL INVESTIGATOR: Robert H. Bartlett, M.D.

CONTRACTING ORGANIZATION: University of Michican Medical Center
Ann Arbor, Michigan 48109-1274

REPORT DATE: January 1998

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	January 1998	Annual (31 Dec 96 - 30 Dec 97)

4. TITLE AND SUBTITLE
Extracorporeal Life Support in Military Casualties

5. FUNDING NUMBERS
DAMD17-97-C-7034

6. AUTHOR(S)
Robert H. Barlett, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Michigan Medical Center
Ann Arbor, Michigan 48109-1274

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200*
The purpose of this contract is to develop a portable extracorporeal life support (ECLS) device and a vascular access system. Part of this project includes the development of a non-thrombogenic surface to allow ECLS with minimal or no system anticoagulation. During the first year of the contract the components for the prototype device have been assembled, the non-occlusive peristaltic pump has been tested in detail, and a non-thrombogenic nitric oxide releasing surface has been developed and tested in our rabbit model.

14. SUBJECT TERMS
Extracorporeal life support, heart-lung machine, vascular access, non-thrombogenic surface, total automation

15. NUMBER OF PAGES
43

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

G ____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

G ____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

____ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

Colin V Dawson 1/22/98

PI - Signature Date

TABLE OF CONTENTS

Annual Report for Contract DAMD 17-97-C-7034
Extracorporeal Life Support in Military Casualties

INTRODUCTION

Extracorporeal life support (ECLS) is the term used for prolonged use of a modified heart-lung machine to sustain life during severe respiratory or circulatory failure. ECLS is widely used for the treatment of children and adults with severe respiratory failure. In addition ECLS is the only mechanical life support system to sustain systemic perfusion during profound circulatory shock. The purpose of this contract is to develop a portable ECLS system which could be used in a far forward military setting.

The requirements for ECLS in this military setting include portable size, automated operation with servoregulation based on physiologic measurements, built in safety features, automatic priming and volume resuscitation, low energy requirement, and minimal or no systemic anticoagulation. Another goal of this project is to develop a quick and simple vascular access system which could be used in the field to achieve ECLS without thoracotomy.

Our research group has studied both basic and clinical application of ECLS for the past 30 years. A non-occlusive peristaltic blood pump developed in our laboratory is ideally suited for automation, safety, and portability applications for military ECLS. Based on this pump and based on our laboratory background in surface thrombogenicity evaluation we were awarded this contract to further develop ECLS for military applications.

As discussed in our original contract proposal, our laboratory has a long history of research on development of ECLS, and has been conducting research on the general topics related to this contract supported by grants from the National Institutes of Health and other sources. Our clinical experience with ECLS, while not supported at all by this contract, has important bearing on further development of ECLS therefore it is discussed in this progress report. All of our laboratory experience, and subcontract activities at MC3 related to this project are summarized in this annual report.

Although the contract start date was January 1, 1997, the expenditure of significant funds from this contract did not begin for a few months while University contract and MC3 subcontract administrative details were being arranged. Because of this we asked Fort Detrick sponsors to change the year 2 and year 3 awards dates to May 1998 and May 1999, with the contract to be completed by May 2000. This request was approved. We will send a supplement to this annual report prior to the next funding cycle May 1, 1998.

Methods And Results

During the past year work on this project was carried out simultaneously in five specific areas: Further development of the pump and pumping systems, development of the small portable ECLS system under subcontract at MC3, development of an anti-platelet non-thrombogenic surface, clinical experience relevant to this contract, and vascular access devices.

Non-Occlusive Peristaltic Pump and Pumping Technology

The unique pump upon which this system is based was developed at Michigan Critical Care Consultants, Inc. (MC3) and tested in our laboratories. University of Michigan holds the patent on this pump which is licensed to MC3 and sub-licensed to Avecor, Inc. of Minneapolis, Minnesota. During this contract year the Avecor version of this pump was approved by the FDA for use in cardiac surgery. This approval is related to this contract only in that it indicates that the FDA approved the pump, the pumping chamber, and the electronics for general use, insuring that potential commercial development in multiple production of the portable ECLS device will be possible. The pump was tested in our laboratories throughout the year in a series of animal experiments which demonstrated that total support of gas exchange is possible using a tidal flow single catheter system in adult-sized animals. This is the first time that total respiratory support with tidal flow has been reported. This demonstrates the applicability of the portable ECLS system using different modes of vascular access for different specific applications. The reference describing this work is listed below. In related experiments a modified ECLS system was used to achieve precise temperature control over a wide range of temperatures in experimental animals. This is particularly important to the military application because hypothermia is a common problem in military casualties, and the ability to warm the subject and maintain precise temperature by perfusion control will be important for ultimate application of the ECLS system. A modified ECLS circuit was also evaluated using a series of hemofilters to clear toxic molecules from the blood in treatment of induced liver failure in animals. Although not addressed in our original contract proposal, the ability to include blood processing for the treatment of fluid overload, renal failure, and multiple organ failure, combined with general cardiopulmonary life support will be a major advantage of this technology. Preliminary report of this work are included in the Appendix.

Development of a Portable Automatic ECLS System

During the first year of the contract this development is subcontracted to MC3. All of the components for the small portable system have been acquired and the basic system has been assembled at MC3. The motor of the pump is smaller than that used for the Avecor cardiac surgery version of the pump. The microprocessor program for automated pump control has been further refined by Dr. Scott Merz of MC3. The development of an automated suction system to allow venous drainage which does not depend on gravity is crucial to the further development of this device. The controlled suction is achieved by encasing the pump chamber in a solid sealed chamber and applying vacuum to the sealed chamber as described in the contract proposal. This system is now assembled and undergoing testing at MC3 to define level of blood flow related to the amount of servoregulated suction. In addition the safety features are being thoroughly evaluated including the possibility of aspiring air with suction, and control of the pump chamber to prevent the possibility of pumping air.

The rapid vascular access system is also under development of MC3. Prototype devices using guide wire access followed by balloon dilatation are being studied and compared to sequential solid dilators as a means of gaining major vascular access.

Non-Thrombogenic Surfaces

Major progress has resulted from the development and evaluation of plastic surfaces which release nitric oxide gas. Nitric oxide gas elaborated from the normal human endothelium inhibits platelet adhesion to endothelial cells. We have taken advantage of this principle in developing a plastic surface which releases nitric oxide. During in-vitro testing using rabbit platelets radio-labeled with ^{111}Indium we have demonstrated that platelet adhesion is remarkably reduced when this compound is incorporated as a plastic coating. We have evaluated this coating in our four-hour ex-vivo rabbit extracorporeal circulation model. This is a very unforgiving model of non-thrombogenic surfaces. Heparin coated surfaces have only minimal favorable effect in this rabbit test model. In our initial testing with nitric oxide releasing surfaces the ex-vivo loops stay patent and platelet count is maintained near normal levels during four hours of extracorporeal circulation. This finding is unprecedented in our laboratory. This indicates that the use of nitric oxide releasing plastics will be a major advance in ECLS, particularly in military applications where hemorrhage and injury make anticoagulation contraindicated. The initial results of these studies were presented at American Society of Artificial Internal Organs (ASAIO) in May 1997. The abstract describing those studies is included in the Appendix. The full manuscript is in preparation. In our continuing studies we plan to evaluate a variety of chemical compounds which liberate nitric oxide and to evaluate controlled release of nitric oxide by evaluating a variety of plastic coating and over-coating techniques. This work is being done in conjunction with MC3 supported by this contract.

While refinement of nitric oxide releasing plastic is underway, we are also evaluating other potential non-thrombogenic surfaces such as phosphorylcholine and heparin bonded surfaces alone and in combination with nitric oxide releasing surface. In addition we are also evaluating other anticoagulant compounds which are specific Factor Xa and IXa inhibitors. These compounds have the potential to achieve anticoagulation without the generalized systemic anticoagulation caused by heparin.

Clinical ECLS

Although no human studies are supported by this contract, our on-going clinical experience is relevant to the military applications of ECLS. Two of our clinical projects during the current year have direct application on this project: venoarterial support for cardiogenic and hemorrhagic shock, and evaluation of the route of vascular access for respiratory support. Our experience with extracorporeal life support as part of cardiopulmonary resuscitation for hemorrhagic and cardiogenic shock was reviewed and reported by John Younger of our group during this year. The abstract of that report is included in the Appendix. Venoarterial access and VA perfusion resulted in approximately 40% survival rate. This is one of the major military applications of ECLS, particularly in far forward positions. This experience demonstrates that the technique is not only feasible but the results of these early trials are encouraging.

At the present time we are evaluating methods of venting the left atrium and left ventricle during venoarterial support in which total cardiac arrest has occurred. In the circumstance bronchial and thebesian venous flow fills the left side of the heart, even during total cardiopulmonary bypass. This results in left ventricular over distention, pulmonary hypertension, and pulmonary edema. This may occur under combat conditions. We have developed a simple

method to vent the left side of the heart and prevent this over distention by transvenous atrial septostomy. This is currently done in the cardiac catheterization lab but we are developing the methodology to do this guided by echocardiography only. This makes the application of ECLS in total cardiac arrest feasible, even in the absence of radiographic equipment.

We have also evaluated two modes of vascular access for respiratory support, right atrium drainage with femoral vein return, and femoral vein drainage with right atrium return. Although our standard clinical practice for several years has been to drain from the right atrium, during the past year we have determined that femoral (inferior vena cava) drainage with internal jugular to right atrial return achieves the same level of total respiratory support at lower blood flow rates, therefore it is a preferable mode of access. Studies were conducted in patients using catheters placed via both routes, comparing the two modes of access. A manuscript describing these observations is in preparation. The tidal flow system described above will be preferable to the dual catheter system once it is developed for clinical use. However for the foreseeable future the observation of the route of venous access will be very important for any application of ECLS in respiratory failure.

Vascular Access

During the past year we have continued to gain clinical experience with percutaneously placed large access catheters for both respiratory and cardiac support. Clinically we are using commercially available sequential solid dilators. As noted above a simpler, quicker balloon dilation system developed under this contract is currently in the prototype stage at MC3.

During this contract year we reported our results with the first 100 adult patients with respiratory failure supported with ECLS. This work was reported to the American Surgical Association by Dr. Kolla. This report and ensuing discussion is included in the Appendix. This report demonstrates that the use of ECLS for respiratory failure in adults is becoming a standard approach in civilian practice.

CONCLUSIONS

The purpose of this contract is to develop a portable extracorporeal life support (ECLS) device and a vascular access system. Part of this development includes the development of a non-thrombogenic surface to allow ECLS machine with minimal or no systemic anticoagulation. During the first year of the contract the components for the prototype device have been assembled, the non-occlusive peristaltic pump has been tested in detail, and a non-thrombogenic nitric oxide releasing surface has been developed and tested in our rabbit model.

REFERENCES

Kolla S, Crotti S, Lee A, Gargulinski MJ, Lewandowski T, Bach D, Hirschl RH, Bartlett RH: Total respiratory support with tidal flow extracorporeal circulation in adult sheep. ASAIO J. 43:M811-M816, 1997.

Kolla S, Awad SA, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH: Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226:544-566, 1997.

Nitric Oxide-Releasing Coating Decreases Platelet Consumption in a Rabbit Model of ECC: GM Annich, S. Merz, J. Meinhardt, B. Ashton, B. Chung, RB Hirschl, RH Bartlett. (Abstract presented at the American Society of Artificial Internal Organs annual meeting May, 1997.)

Systemic Hyperthermia Induced by Venoarterial Perfusion for Cancer Therapy: O. Soldes, S. Award, P. Rich, W. Lynch, J. Younger, R. Hirschl, R. Bartlett. (Abstract submitted for presentation at the American Society of Artificial Internal Organs annual meeting April, 1998.)

Evaluation of an Extracorporeal Liver Assist Device Utilizing Selective Hemodiafiltration in an Animal Model of Hepatic Failure: S. Awad, O. Soldes, S. Sawada, P. Rich, M. Gargulinski, S. Mahler, R. Hirschl, R. Bartlett. (Abstract submitted for presentation at the American Society of Artificial Internal Organs annual meeting April, 1998.)

Outcome Following Extracorporeal Resuscitation: J. Younger, R. Schreiner, R. Hirschl, R. Chapman, R. Bartlett. (Presented at the European Extracorporeal Support Organization Annual Scientific Meeting Oxford, England, August 1997.)

APPENDICES

Evaluation of an Extracorporeal Liver Assist Device Utilizing Selective Hemodiafiltration in an Animal Model of Hepatic Failure: S. Awad, O. Soldes, S. Sawada, P. Rich, M. Gargulinski, S. Mahler, R. Hirschl, R. Bartlett.

Outcome Following Extracorporeal Resuscitation: J. Younger, R. Schreiner, R. Hirschl, R. Chapman, R. Bartlett.

Systemic Hyperthermia Induced by Venoarterial Perfusion for Cancer Therapy: O. Soldes, S. Award, P. Rich, W. Lynch, J. Younger, R. Hirschl, R. Bartlett.

Nitric Oxide-Releasing Coating Decreases Platelet Consumption in a Rabbit Model of ECC: GM Annich, S. Merz, J. Meinhardt, B. Ashton, B. Chung, RB Hirschl, RH Bartlett.

Kolla S, Awad SA, Rich PB, Schreiner RJ, Hirschl RB, Bartlett RH: Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226:544-566, 1997.

Kolla S, Crotti S, Lee A, Gargulinski MJ, Lewandowski T, Bach D, Hirschl RH, Bartlett RH: Total respiratory support with tidal flow extracorporeal circulation in adult sheep. ASAIO J. 43:M811-M816, 1997.

EVALUATION OF AN EXTRACORPOREAL LIVER ASSIST DEVICE UTILIZING SELECTIVE HEMODIAFILTRATION IN AN ANIMAL MODEL OF HEPATIC FAILURE

INTRODUCTION: Clearance of toxins, that have been implicated as a cause of hepatic encephalopathy and coma, has been proven effective *in vitro*, using an extracorporeal liver assist device (ECLVS), which utilizes hemodiafiltration with albumin dialysis.

OBJECTIVE: To evaluate the safety and efficacy of ECLVS in an animal model of hepatic failure. We hypothesized that continuous veno-venous hemodiafiltration with albumin dialysis would: 1) decrease elevated levels of total bilirubin and ammonia, 2) reverse the ratio of branched chain to aromatic amino acids (Fisher ratio), and 3) maintain stable blood pressure and heart rate.

METHODS: Nine mongrel dogs underwent common bile duct transection and an end to side portocaval shunt. On post operative day 7, with continuous monitoring of blood pressure and heart rate, each dog underwent hemodiafiltration for six hours using a 10 % albumin dialysate solution. Blood samples were collected before and after treatment and evaluated for total bilirubin, ammonia, aromatic and branched chain amino acids, pH, potassium, calcium, and bicarbonate levels. Comparisons were made using ANOVA and paired Student's t test.

Table 1- Before And After Six Hours of Treatment (n=9)

Variable	Pre ECLVS	Post ECLVS	p
Blood Pressure	110±17/ 60± 20	121± 26 / 69± 19	0.32
Heart Rate	119± 34	139 ± 49	0.11
Ammonia	17± 99	119 ± 80	0.01
Total Bilirubin	4.5± 2.3	2.92 ± 1.47	0.003
Fisher Ratio	1.67± 0.42	2.15 ± 0.42	0.012

RESULTS: All animals survived treatment with stable hemodynamics. The total bilirubin, and ammonia levels significantly decreased by 35 and 34% respectively, while the Fisher ratio significantly increased from their initial values (Table 1).

CONCLUSION: An extracorporeal liver assist device which utilizes selective hemodiafiltration with albumin dialysis is effective in clearing ammonia, aromatic amino acids, and bilirubin in an animal model of hepatic failure. This sets the stage for clinical investigation.

OUTCOME FOLLOWING EXTRACORPOREAL RESUSCITATION.

JG Younger, RJ Schreiner, RB Hirschl, RA Chapman, RH Bartlett,
University of Michigan, Ann Arbor, MI, USA.

Extracorporeal support of heart and lung function during cardiac arrest offers the rapid return of oxygenation and cardiac output to patients not responding to traditional CPR. We reviewed the pediatric and adult patients treated at our institution with this therapy. Patients were considered candidates for therapy if CPR was required or deemed imminent either prior to presentation to the emergency department or during hospitalization. Patients were excluded if they suffered any comorbid condition felt to preclude a meaningful recovery. ECPR was typically instituted using femoral venous to femoral arterial bypass, and was continued until patients either regained sufficient cardiopulmonary function to allow weaning or until their condition was felt to be irrecoverable. During the 5 year study period, requests for ECPR were made in 17 patients, all of whom were treated. Nine patients successfully regained independent cardiopulmonary function, 8 of whom had normal neurologic function. Of these, 6 were long term survivors. Age was similar in survivors (mean 34 y, range 22 - 55) and nonsurvivors (mean 34 y, range 1.5 - 64). Survivors were treated with extracorporeal support on average 44 hours (range 21-68 hours) and nonsurvivors 34 hours (range 48 min. - 146 hours). In 5 of the 8 never regaining consciousness, support was discontinued within 1 hour of its initiation. Survival was seen exclusively in patients with massive pulmonary embolus or other promptly treatable abnormality. Conclusion: ECPR provided 47% neurologic recovery and 37% long term survival in a small subset of cardiac arrest victims at our institution.

Presented, 1997 European Extracorporeal Support Organization Annual Scientific Meeting, Oxford, England.

SYSTEMIC HYPERTHERMIA INDUCED BY VENOARTERIAL PERFUSION FOR CANCER THERAPY

Systemic hyperthermia (SH) is being investigated for the treatment of metastatic cancer. Neoplastic cells are killed by temperatures of 41.5° C and above. The temperature distribution induced by a venoarterial perfusion system for SH was determined. The safety and biochemical effects of the system were also evaluated. Five 15 - 20 kg dogs were anesthetized and mechanically ventilated. Temperature probes were placed in the rectum, esophagus, bladder, pulmonary artery (PA), proximal aorta (Ao), and tympanic canal. Right atrial to right femoral artery venoarterial bypass at 30 ml/kg/min was established. The perfusate was warmed by a heat exchanger to 42.0 - 43.3° C. The dogs' rectal temperature was maintained at $\geq$ 42° C (42 - 42.8° C) for 90 minutes. All dogs tolerated the perfusion and were without significant side effects one week post-perfusion. A caudad to cephalad body temperature gradient was established, with the rectal temperature 1.1 - 0.2° C above that in the proximal aorta or pulmonary artery. The temperature gradient narrowed with increasing perfusion time. Modest biochemical changes were observed after perfusion (table).

	Baseline	Post - SH	7 Days Post - SH
Sodium (mEq/L)	148.2 ± 1.0	147.9 ± 0.3	
Potassium (mEq/L)	3.67 ± 0.10	4.19 ± 0.10 *	
Calcium, Ionized (mg/dl)	1.40 ± 0.04	1.07 ± 0.01 *	
Bicarbonate (mEq/dl)	24.6 ± 1.2	17.0 ± 1.1 *	
BUN (mg/dl)	16 ± 3	16 ± 3	26 ± 4
Glucose (mg/dl)	99 ± 3	94 ± 5	
AST (U/L)	18 ± 3	38 ± 18	16 ± 7
ALT (U/L)	43 ± 11	40 ± 5	42 ± 7
Alkaline Phosphatase (U/L)	60 ± 11	65 ± 20	256 ± 80
Albumin (g/dl)	2.8 ± 0.0	1.9 ± 0.1 *	3.2 ± 0.1
HCT (%)	36 ± 1	28 ± 3 *	28 ± 3 *

± SEM, *: $p<0.05$ vs. baseline

These results suggest that this perfusion system is well-tolerated and the heating pattern induced by it is suited for the treatment of pelvic malignancies.

O. Soldes, S. Awad, P. Rich, W. Lynch, J. Younger, R. Hirschl, R. Bartlett.
University of Michigan Medical School.

NITRIC OXIDE-RELEASING COATING DECREASES PLATELET CONSUMPTION
IN A RABBIT MODEL OF ECC

A nitric oxide (NO)-releasing coating was investigated to determine its ability to reduce platelet activation and adhesion in extracorporeal circulation (ECC). In vitro and in vivo studies in New Zealand White rabbits were performed.

In the in vitro study, platelet adhesion was tested on coated and uncoated polypropylene tubes. The coatings tested were polyvinyl chloride (PVC) and PVC plus N,N'-dimethylhexanediamine nitric oxide adduct (DMHD/NO), a compound that releases NO upon reaction with water. PPP and glass tubes were used as controls. Rabbit platelets were separated, labeled with ^{111}I, and resuspended in plasma. (PRP); 2 ml aliquots of PRP were incubated in test tubes at 37°C for 1 hour. Following incubation, the tubes were gently rinsed in Hepes buffer solution and placed in a gamma counter. ANOVA and posthoc analysis with Bonferroni correction for multiple comparisons ($p<0.05$) showed less radioactivity in the DMHD/NO tubes as compared to PVC or PPP. The in vivo study used an ECC circuit composed of 1m of PVC tubing, 2 polycarbonate connectors and 2 PVC access cannulas. The circuit was coated with a thin layer of DMHD/NO suspended in a solution of PVC tubing. Three rabbits were anes-thetized, ventilated, heparinized, and injected with ^{111}I-labeled platelets. They were then placed on the ECC test circuits via roller pump, for 4 hours at 37°C. Baseline and hourly blood samples were drawn for platelet counts.. After 4 hours, the circuit was cut into 5 cm segments and placed in a gamma counter. Platelet consumption was compared to control experiments that used uncoated tubing. Platelet count dropped by 45% in the controls and 8.3% in the test animals. Despite the small sample size, (N=3)in the test group, this difference was significant at a $p<0.05$ and a power of 80%. There was no difference in circuit radioactivity. and there were no noticeable adverse physiologic reactions to the test circuits; methemoglobin levels did not rise above 2%.

The NO-releasing coating is effective in decreasing platelet adhesion and consumption in the rabbit model of ECC.

GM Annich, S Merz, J Meinhardt, B Ashton, B Chung, RB Hirschl, RH Bartlett
University of Michigan and MC3 Inc.

Reprinted from: ANNALS OF SURGERY, Vol. 226, No. 4, October 1997

Extracorporeal Life Support for 100 Adult Patients With Severe Respiratory Failure

Srinivas Kolla, M.D., Samir S. Awad, M.D., Preston B. Rich, M.D.,
Robert J. Schreiner, M.D., Ronald B. Hirschl, M.D., Robert H. Bartlett, M.D.

ANNALS OF SURGERY
Vol. 226, No. 4, 544–566

Extracorporeal Life Support for 100 Adult Patients With Severe Respiratory Failure

Srinivas Kolla, M.D., Samir S. Awad, M.D., Preston B. Rich, M.D., Robert J. Schreiner, M.D., Ronald B. Hirschl, M.D., Robert H. Bartlett, M.D.

From the Department of Surgery, University of Michigan Medical Center, Ann Arbor, Michigan

Objective

The authors retrospectively reviewed their experience with extracorporeal life support (ECLS) in 100 adult patients with severe respiratory failure (ARF) to define techniques, characterize its efficacy and utilization, and determine predictors of outcome.

Summary Background Data

Extracorporeal life support maintains gas exchange during ARF, providing diseased lungs an optimal environment in which to heal. Extracorporeal life support has been successful in the treatment of respiratory failure in infants and children. In 1990, the authors instituted a standardized protocol for treatment of severe ARF in adults, which included ECLS when less invasive methods failed.

Methods

From January 1990 to July 1996, the authors used ECLS for 100 adults with severe acute *hypoxemic* respiratory failure (n = 94): p_aO_2/F_iO_2 ratio of 55.7 ± 15.9, transpulmonary shunt (Qs/Qt) of 52 ± 22%, or acute *hypercarbic* respiratory failure (n = 6): p_aCO_2 84.0 ± 31.5 mmHg, despite and after maximal conventional ventilation. The technique included venovenous percutaneous access, lung "rest," transport on ECLS, minimal anticoagulation, hemofiltration, and optimal systemic oxygen delivery.

Results

Overall hospital survival was 54%. The duration of ECLS was 271.9 ± 248.6 hours. Primary diagnoses included pneumonia (49 cases, 53% survived), adult respiratory distress syndrome (45 cases, 51% survived), and airway support (6 cases, 83% survived). Multivariate logistic regression modeling identified the following pre-ECLS variables significant independent predictors of outcome: 1) pre-ECLS days of mechanical ventilation ($p = 0.0003$), 2) pre-ECLS p_aO_2/F_iO_2 ratio ($p = 0.002$), and 3) age (years) ($p = 0.005$). Modeling of variables during ECLS showed that no mechanical complications were independent predictors of outcome, and the only patient-related complications associated with outcome were the presence of renal failure ($p < 0.0001$) and significant surgical site bleeding ($p = 0.0005$).

Conclusions

Extracorporeal life support provides life support for ARF in adults, allowing time for injured lungs to recover. In 100 patients selected for high mortality risk despite and after optimal

conventional treatment, 54% survived. Extracorporeal life support is extraordinary but reasonable treatment in severe adult respiratory failure. Predictors of survival exist that may be useful for patient prognostication and design of future prospective studies.

Extracorporeal circulation with a mechanical pump oxygenator provides temporary life support allowing cardiac operations. Modifications in the techniques and devices allow prolonged extracorporeal circulation in the intensive care unit (ICU), commonly referred to as extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS). For the past decade, ECLS has been standard treatment for newborn infants with severe respiratory failure (ARF) unresponsive to other methods of treatment. Extracorporeal life support has been used for >10,000 newborn infants with 80% survival from what was once a lethal condition.[1] The neonatal technique has been modified for use in older children with similar success in experienced centers.[2]

The use of ECLS in adult patients with ARF has been less encouraging. The first successful case was reported by Hill et al.[3] in 1971 followed by a series of case reports.[4] A randomized multicenter trial[5] of venoarterial (VA) ECMO in 1975 to 1978 yielded only 10% survival in both the ECMO and conventional treatment groups. In 1986, Gattinoni et al.[6] reported 49% survival with extracorporeal carbondioxide removal ($ECCO_2R$), a modified ECLS technique using venovenous (VV) access with low blood flow to permit carbon dioxide (CO_2) removal, ''resting'' the lung from high pressure and high-inspired oxygen, but relying on the native lung for oxygenation. This report changed the practice of mechanical ventilation worldwide by identifying the beneficial effects of avoiding high-pressure overdistention of the lung and renewed interest in ECLS for adult respiratory failure. Other centers have corroborated these results, resulting in 30% to 40% survival from ARF with improved conventional management,[7] 40% to 50% survival with ECLS,[8] and 50% to 60% survival with the two combined.[9–11]

Based on our experience with neonatal and pediatric ECMO,[12,13] and encouraged by the European results with $ECCO_2R$, we initiated a clinical trial in 1988 consisting of a management protocol for severe ARF that included pressure-controlled inverse ratio ventilation, optimized systemic oxygen delivery, restoration of dry weight, prone positioning, and ECLS. After 2 years of pilot experience and protocol modification, we have followed this standardized approach since 1990. We have reported the results of the ECLS group at regular intervals.[14–17] During this time, we used VA ECLS for circulatory shock secondary to cardiac failure, pulmonary embolism, and anaphylaxis in 16 patients.[18] This is a report of 100 consecutive adult patients treated with ECLS for ARF since the beginning of our standardized protocol. This report is undertaken to describe the evolution and current details of the technique, to characterize the results in a diverse group of patients with ARF, and to determine predictors of outcome for individual patient prognostication and for the design of a prospective, comparative study.

PATIENTS AND METHODS

Between January 1990 and July 1996, 141 patients were referred for ECLS for severe ARF from outside institutions or from other services in our own medical center. Forty-one patients improved with conventional treatment; 100 patients failed to improve and were treated with ECLS. These patients form the basis for this study. Data were abstracted from patient records and bedside ECLS flow sheets.

Selection Criteria

The original selection criteria we used for ECLS were the following: transpulmonary shunt >30%, compliance <0.5 mL/cm water/kg, mechanical ventilation <5 days, and age younger than 60 years of age. These indications were defined to identify a group of patients with very high mortality risk but significant potential for lung recovery and survival. The 30% shunt measurement of hypoxemic respiratory failure was designated to paraphrase the ''slow and fast entry criteria'' from the 1975 to 1978 National Institutes of Health ECMO study.[5] (The exact entry criteria for that study corresponded to 30% shunt, but required decreasing positive end-expiratory pressure (PEEP) and inspired oxygen concentration (F_iO_2) to determine whether the arterial oxygen tension (p_aO_2) would be <50 mmHg at certain settings, which was dangerous, so we devised selection criteria that could be measured during any phase of treatment.) Shunt calculation requires mixed venous blood sampling, which is not always available. Shunt fraction <30% corresponds to a p_aO_2/F_iO_2 ratio <100 or alveolar-arterial oxygen gradient ($A\text{-}aDO_2$) >500. The compliance indicator included disordered pulmonary mechanics in the indications. It is important to emphasize that these physiologic indicators of ARF were

Presented at the 117th Annual Meeting of the American Surgical Association, Quebec City, Quebec, Canada, April 17–19, 1997.
Supported in part by a grant from the National Institutes of Health.
Address correspondence and reprint requests to Robert H. Bartlett, M.D., University of Michigan Medical Center, 1500 E. Medical Center Drive, 2918 Taubman Center, Box 0331, Ann Arbor, MI 48109-0331.
Accepted for publication April 23, 1997.

measured *despite and after* optimal treatment, so they represent the best-case rather than the worst-case physiologic status. Age and ventilator days criteria arbitrarily were defined to identify a group of patients with reasonable chance of ultimate recovery. Initially, contraindications to ECLS included age older than 60 years, ventilator days >5, evidence of irreversible brain injury, incurable disease, immunosuppressive therapy, and septic shock. As our experience progressed, we accepted patients with >5 days of mechanical ventilation, immunosuppressive treatment, and septic shock to gain experience in these categories.

Our standardized protocol[19,20] for hypoxemic respiratory failure includes the following: 1) time-cycled, pressure-limited, mechanical ventilation with prolonged inspiratory time; 2) end inspiratory (plateau) pressure limited to 40cm water (accepting hypercarbia if hypoventilation resulted from this pressure limit); 3) best PEEP based on mixed venous saturation; 4) F_iO_2 limited to 0.6 (accepting hypoxemia [S_aO_2 85%–90%] if it resulted from this limitation); 5) monitoring the oxygen delivery to consumption ratio [DO_2/VO_2] by mixed venous saturation; 6) optimizing DO_2/VO_2 >4 by transfusion to normal hematocrit, PEEP, and F_iO_2 titration, inotropes, if necessary, and sedation and paralysis to decrease VO_2; 7) optimization of ventilation–perfusion (V/Q) matching and alveolar recruitment by prone positioning; 8) diuresis to dry weight; and 9) full nutritional support based on metabolic balance measurements.

Selection criteria for hypercarbic respiratory failure included the presence of life-threatening anatomic airway obstruction, status asthmaticus unresponsive to maximum pharmacologic intervention, and uncorrectable hypercarbia with pH <7 and end-inspiratory pressure >45 mmHg.

Transport and Emergency Extracorporeal Life Support

During the pilot phase of our experience, several young salvageable patients died during attempted transfer or shortly after arrival to our ICU. Because of this, we developed a portable ECLS system, so that ECLS could be initiated in the referral hospital ICU, permitting stable elective transfer. This system also was used for emergency use in our hospital when ARF was complicated by sudden hypotension, arrhythmia, or cardiac arrest.

Methods of Extracorporeal Life Support

Management of ECLS requires detailed protocols, an experienced team of physicians, nurses, therapists, and ECLS specialists, hospital-wide support services, and special equipment and supplies. All of these elements are described in detail elsewhere[21] and are summarized here briefly.

Vascular Access

Venovenous access was the preferred method of access as long as cardiac function was adequate. Venous drainage was achieved by cannulation of the right atrium via the right internal jugular vein. Arterialized blood was returned through cannulation of the right or left femoral vein. Early in our experience, we performed all cannulation by direct cutdown access. Since 1992, we have placed cannulas by percutaneous access using the Seldinger technique. However, if the cannula could not be placed or if there were complications during percutaneous placement, direct cutdown access was undertaken.

Venoarterial access was undertaken when there was combined profound cardiac and respiratory failure. Requirement for inotropes was not an absolute indication for VA ECLS. In many cases, institution of VV ECLS allowed improvement in cardiac function without the need for VA support. Before 1992, we used VA access for all transport patients. Since then, we have successfully transported patients with VV access.

Venoarterial support was established by direct cutdown access. Drainage typically was accomplished from the right atrium via the right internal jugular vein, whereas arterial access usually was gained through the right common carotid artery, which was ligated distally. Additional or alternative drainage sites include the right or left femoral vein, and alternative infusion sites included the right or left femoral arteries. The femoral artery was chosen only when some lung function remained and aortic root blood could be oxygenated successfully; otherwise, the choice of the right common carotid was undertaken to ensure adequate perfusion and oxygenation in the proximal aorta. When the femoral artery was cannulated by cutdown, the distal artery was perfused via a separate cannula. Recently, we have used percutaneous femoral artery access without distal perfusion. If, during support with established VV access, there was evidence of cardiac failure unresponsive to moderate doses of inotropes, VV access was converted to VA access. In addition, if a patient was receiving VA access for transporting the patient or because of severe hemodynamic instability, the patient was converted to VV access once adequate myocardial function was shown.

Extracorporeal Life Support Circuit

Our standard adult ECLS circuit consisted of two solid silicone rubber membrane lungs (4.5 m^2 spiral coiled oxygenator) in parallel, a servoregulated occlusive roller pump, and a heat exchanger. Circuit monitors included an online mixed venous saturation monitor in the venous drainage line, preoxygenator and postoxygenator pressure monitors, flow measurement, and a device for measuring whole blood clotting time. Our emergency and transport

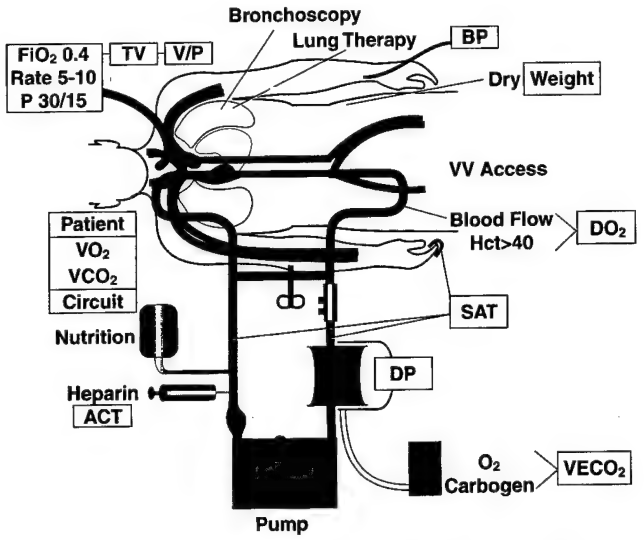

Figure 1. Summary of the protocol for treatment and monitoring of severe respiratory failure in adults. For venovenous extracorporeal life support, venous blood is drained from the right atrium via the internal jugular vein. Blood is pumped through an oxygenator and a heat exchanger where carbon dioxide is removed, blood is oxygenated, warmed, and returned to the venous circulation via the femoral vein. During venoarterial extracorporeal life support, the blood is most often returned to the arterial circulation via the right common carotid artery. Hemodynamic and metabolic parameters that are monitored continuously are shown in rectangles. VV = venovenous; DO_2 = oxygen delivery; VO_2 = oxygen consumption; VCO_2 = carbon dioxide production; V_ECO_2 = oxygenator outlet carbon dioxide concentration; ACT = activated clotting time; Hct = hematocrit; F_IO_2 = inspired oxygen concentration; TV = tidal volume; V/P = volume/pressure, compliance; SAT = percent saturation of hemoglobin by oxygen; DP = pressure drop across membrane oxygenator.

circuit differed from our standard circuit only in that we used a centrifugal pump and a single membrane oxygenator to make the circuit more compact.

Patient Management on Extracorporeal Life Support

Our approach to patient management on ECLS is shown in Figure 1. Once ECLS was initiated, the ventilator was adjusted to "rest" settings $F_IO_2 \leq 0.5$, end inspiratory pressure ≤35, PEEP 10 to 15, rate 4 to 6/minutes I:E 2 to 4:1. Thereafter, the ECLS flow was maintained to sustain a venous blood saturation at 80% to 85% and arterial saturation of 80% to 90% (typically, 50–70 mL/kg per minute). All patients were monitored with an indwelling arterial catheter and an Oximetrix (Mountain View, CA) pulmonary artery catheter. Blood carbon dioxide was regulated by adjusting the sweep gas flow rate to the membrane lungs to keep arterial carbon dioxide tension (p_aCO_2) approximately 40 mmHg. Packed erythrocytes were transfused to maintain the hematocrit 45% to 48% to facilitate oxygen delivery and ease the requirement for high extracorporeal flow. Inotropes usually were discontinued within 24 to 48 hours. Oxygen consumption was minimized by paralysis, sedation, and mild hypothermia (35–36 C) as needed to optimize the oxygen delivery to consumption ratio.

During bypass, standard vital signs were monitored, including pulmonary artery pressure, systemic and mixed venous saturation, end-tidal CO_2, ventilator pressures and tidal volume, urine output, and daily weight. Hematocrit, creatinine and bilirubin, and blood gases were measured daily. Thermodilution cardiac output was measured using a modified catheter, which has an injection port in the right ventricle, accepting that with this technique, some tricuspid regurgitation and false values were possible.

Pulmonary function was assessed by monitoring the difference in saturation between venous blood (pulmonary artery and venous drainage), and systemic arterial blood, the end-tidal CO_2, and an index of static lung compliance (Tidal Volume/peak inspiratory pressure [PIP] − PEEP). Standard treatment for severe lung dysfunction was continued during ECLS, including bronchoscopy, when necessary, prone positioning, and diuresis to dry weight. Chest x-rays were made daily.

Tracheostomy usually was undertaken on the first or second day of ECLS to decrease the incidence of nosocomial pneumonia, ease access to the airway, and aid in ventilator weaning. In our early experience, we performed open tracheostomy, but since 1992, performed this procedure by percutaneous access.

Hemodynamics and cardiac status was monitored by pulse contour, pulmonary capillary wedge pressure, thermodilution cardiac output, systemic blood pressure, and signs of systemic perfusion. Echocardiography was undertaken if further evaluation of cardiac function was necessary.

Nutrition was managed by initiating early enteral feeding or total parenteral nutrition when enteral route was not possible. Caloric support was provided based on indirect calorimetry, and protein support was provided based on direct measurements of total nitrogen loss.

Diuretics were given if needed to maintain adequate urine output and remove excess fluid to maintain the patient at dry weight (preillness weight). If negative fluid balance could not be achieved with diuretics, a hemofilter was added to the ECLS circuit.

Often the neurologic status of patient was uncertain at the time of initiation of ECLS. Once patients were stable receiving ECLS, sedation and paralysis were discontinued until the status of brain function was documented. Although patients did not necessarily return to normal consciousness, we expected spontaneous movement of all extremities, eyes, and tongue as well as the ability to follow simple commands. Once this level was verified, patients were allowed to remain awake and alert as possible, with sedation titrated to apparent patient comfort.

Paralysis only was used to allow tolerance of prolonged inspiration time ventilation strategies or to diminish excessive oxygen consumption due to patient agitation or activity to levels that could be matched by ECLS-based oxygen delivery. If patients remained paralyzed and sedated, agents were reversed every 24 to 48 hours to reassess neurologic function. Head computed tomographic scanning was undertaken with low threshold if there was sustained significant decrease in brain function during interval assessments. Extracorporeal life support was discontinued if there was evidence of severe neurologic injury.

In treating patients with primary hypercarbic respiratory failure due to status asthmaticus or airway obstruction, low flow ECLS (15–30 mL/kg per minute) was used for carbon dioxide removal. This permitted decreasing ventilator settings to low nondamaging ventilator settings, allowing resolution of high-intrathoracic pressures and cardiovascular collapse and prevention of further barotrauma. Bronchoscopy, lung lavage, and direct airway management then were performed.

Anticoagulation and Bleeding

Systemic anticoagulation was maintained with heparin continuously infused to maintain the whole blood activated clotting time (ACT) 160 to 180 seconds (upper limit of normal is 120 seconds). Platelets were transfused to maintain the platelet count 80,000 to 100,000/mm^3. Bleeding was managed by decreasing heparin to achieve an ACT of 140 to 160 seconds, transfusing platelets until the count was >100,000/mm^3, infusing blood products as needed, including fresh frozen plasma and cryoprecipitate, and locally exploring surgical sites as necessary. Aprotinin or aminocaproic acid occasionally was used for bleeding in the chest, peritoneum, and brain. Bleeding from the gastrointestinal tract or the lung parenchyma was treated aggressively with endoscopy or bronchoscopy as was possible. Ultimately, however, intractable bleeding (not corrected within a few hours or excessive bleeding) was corrected by surgical intervention with definitive control of bleeding sites.

Weaning and Decannulation

Native lung oxygen consumption (VO_2), carbon dioxide production (VCO_2), as well as membrane lung VO_2, VCO_2 were measured daily. These measurements allowed us to calculate the percentage of total VO_2 achieved by the native lung (as well as for nutritional planning). Lung recovery was signaled by a step increase in VO_2 achieved by the native lung as well as by a step increase in saturation between pulmonary arterial and systemic arterial saturations. When native lung function improved, ECLS flow was decreased until the native lung was supporting 50% to 80% of total gas exchange, then a trial off ECLS was undertaken. If gas exchange and hemodynamics were adequate at ventilator settings $F_iO_2 \leq 0.5$ and PIP ≤ 35-cm water, and PEEP ≤10-cm water, ECLS was discontinued and vascular access catheters removed. In the case of percutaneously placed venous or arterial catheters, the catheters simply were removed and pressure held over the cannulation site, whereas in the case of catheters placed by direct cutdown access, the catheters were removed under direct visualization and the vessels ligated, except for the femoral artery, which was repaired.

Weaning From the Ventilator

Continued ventilator management after ECLS consisted of maintaining the patient as awake as possible, continuing prone position, and weaning down to low ventilator settings as rapidly as possible. Because of prolonged ICU and hospital course, patients often underwent a course of rehabilitation before hospital discharge to regain functional status.

Futility

It is difficult to recognize when continuing treatment is futile in any ICU patients and particularly difficult during ECLS. Extracorporeal life support sustains vital functions far beyond the point of otherwise fatal organ failure, and often these organs recover. However, ECLS should be stopped when there is no hope of recovery.

Although there are no definite criteria to indicate the irreversibility of ARF, we use certain guidelines to determine when to terminate support in the clinical context of individual patients: 1) total fibrosis by open lung biopsy or in conjunction with the clinical finding of a fixed mean pulmonary artery pressure to mean arterial pressure ratio >0.67 and lack of demonstrable lung function; 2) advanced multiple organ system failure; 3) septic shock unresponsive to pharmacologic measures; 4) uncontrollable intrapulmonary hemorrhage; and 5) severe irreversible brain damage or demonstrable lack of neurologic function determined both clinically and by diagnostic methods.

In general, cause of death during ECLS or after ECLS was determined by autopsy; however, when that was not possible, the cause of death was ascribed to the treating physicians' assessment of the cause of death. All survivors were observed long term and functional disability was assessed.

Complications

Mechanical complications were compiled on an occurrence basis and related to the devices that comprise the ECLS circuit. Physiologic complications were compiled similarly and are characterized as hemorrhagic, neuro-

logic, cardiac, pulmonary, infectious, renal, and hepatic. Complications were coded at the end of ECLS for each patient.

Data Presentation and Analysis

The reason for ARF was classified as hypoxemic (94 patients) or hypercarbic (6 patients) respiratory failure. All patients with hypoxemic respiratory failure had adult respiratory distress syndrome (ARDS) according to the consensus conference[22] or any other[23,24] definition. Reports of "ARDS" in the literature may or may not include ARF from primary pulmonary parenchymal disease such as pneumonia or vasculitis. We classified proven or presumed primary lung infection or aspiration as "pneumonia with ARDS." All others were classified as ARDS due to such things as trauma, vasculitis, and sepsis. The severity of ARF and concomitant organ dysfunction is variably reported in the literature, including worst-case condition on the first day of ICU care,[22,25] worst-case condition at the time of referral,[26,27] condition throughout the ICU course,[24,28] or some combination.[29] We listed the p_aO_2/F_iO_2 ratio and shunt just before ECLS, despite and after optimal treatment. During the ICU course, all patients with hypoxemia had Murray lung score = 4,[28] Geneva lung score = 4,[30] and Massachusetts General Hospital lung score severe.[31]

Although important in prognostication, the definition of sepsis is elusive, particularly because temperature, metabolic rate, and blood pressure are controlled during ECLS, and leukocytosis and thrombocytopenia are related to the procedure. All of the pneumonia patients and most of the ARDS patients in this series had "sepsis" indicators at the time of referral, but hemodynamic instability was caused by a combination of infection and high intrathoracic pressure. Accordingly, we reserved "sepsis" designation for patients with positive blood cultures associated with hemodynamic instability.

Patients requiring ECLS before our protocol could be initiated (transport or urgent patients) were classified as *moribund.* Patients who were treated with our optimal treatment protocol but who did not respond were classified as ">12 hours, University of Michigan protocol."

Statistical Analysis

All values are reported as mean values with standard deviation. Multivariate logistic regression analyses were performed to determine the effect of pre-ECLS variables and variables during ECLS on survival. Stepwise procedure using a significance level of 0.05 was used to enter or remove variables from the models. Estimated coefficients for independent variables (β), standard errors, chi square of the maximum likelihood Wald test, and odds ratio are described. All statistical analyses were performed with the SAS statistical package (SAS Institute Inc, Cary, NC).

Table 1. PATIENT CHARACTERISTICS FOR ADULT RESPIRATORY ECLS

	Hypoxemic Respiratory Failure (n = 94)	Hypercarbic Respiratory Failure (n = 6)
Survival/recovery (%)	(52.1/59.6)	(83.0/83.0)
Male/female (%)	(46.8/53.2)	(33.3/66.7)
Weight (kg)	77.6 ± 22.2	73.0 ± 17.5
Age (yr)	33.9 ± 12.5	37.8 ± 9.3
Duration of ECLS (hr)	285.3 ± 249.9	54.0 ± 41.5
p_aO_2/F_iO_2 ratio	55.7 ± 16.0	266.2 ± 161.8
Shunt (Q_s/Q_t)	0.52 ± 0.22*	0.25 ± 0.20
Pre-ECLS vent days	3.5 ± 2.7	3.8 ± 4.3
Last pre-ECLS ABG		
p_aO_2 (mmHg)	54.7 ± 15.0	187.5 ± 158.0
p_aCO_2 (mmHg)	45.4 ± 12.3	84.0 ± 31.5
pH	7.26 ± 0.76	7.19 ± 0.18
S_aO_2 (%)	82.0 ± 12.0	95.0 ± 7.5
Last pre-ECLS ventilator settings		
F_iO_2	1.00 ± 0.10	0.70 ± 0.30
PIP (cmH_2O)	46.5 ± 13.4	51.3 ± 9.9
PEEP	13.9 ± 4.8	2.2 ± 3.5
S_vO_2	49.8 ± 21.5*	72.2 ± 12.5

ECLS = extracorporeal life support; F_iO_2 = fraction inspired oxygen; Q_s/Q_t = fraction of pulmonary shunt to total pulmonary blood flow; ABG = arterial blood gas; S_aO_2 = arterial oxygen saturation, PIP = peak inspiratory pressure; PEEP = positive end-expiratory pressure; S_vO_2 = mixed venous oxygen saturation. Survival is defined as discharge from hospital. Data are reported means ± SD.
* n = 81.

RESULTS

Between January 1990 and July 1996, 141 patients with ARF unresponsive to conventional treatment were referred for ECLS from outside institutions (78 patients) or from within our own medical center (22 patients). Of these patients, 75 patients were unstable and required ECLS urgently (moribund classification); 33 of these patients were transported on ECLS. Sixty-six patients were stable enough to be treated in our ICU after our optimal therapy protocol. Forty-one of these patients improved and 25 did not, requiring institution of ECLS within 12 to 48 hours. In total, 100 patients with ARF underwent treatment with ECLS. The entire patient group is described in Appendix 1.

Of 141 patients referred for ECLS, 62% survived. Of 100 ECLS patients, 62 weaned from ECLS and 54 survived to discharge. Forty-four of the 75 cases classified moribund sur-

Table 2. PERCENT SURVIVAL BY PRIMARY DIAGNOSIS FOR ADULT RESPIRATORY ECLS

	% (number)
Hypoxemic respiratory failure	52 (49/94)
Pneumonia	53 (26/49)
Bacterial	50 (12/24)
Viral*	59 (13/22)
Aspiration	50 (1/2)
Protozoan	0 (0/1)
ARDS	51 (23/45)
Trauma	50 (9/18)
Sepsis	57 (4/7)
Other	50 (10/20)
Lung transplant	40 (2/5)
Vasculitis, BOOP	40 (2/5)
Pancreatitis	67 (2/3)
Postoperative cardiac surgery	50 (1/2)
Liver failure	100 (1/1)
Cocaine inhalation	0 (0/1)
Laryngospasm	100 (1/1)
Unknown etiology	50 (1/2)
Hypercarbic respiratory failure	83 (5/6)
Status asthmaticus	75 (3/4)
Tracheal obstruction	100 (2/2)

ECLS = extracorporeal life support; ARDS = adult respiratory distress syndrome; BOOP = bronchiolitis obliterans organizing pneumonia.
* Diagnosis based on culture proven viral infection or presumptively based on clinical findings.

vived, including 24 of the 33 patients transported receiving ECLS. Ten of 25 patients who did not improve on our protocol and who required ECLS survived.

Overall characteristics are listed in Table 1. Ninety-four patients with hypoxemic respiratory failure had an average age of 33.9 ± 12.5 years, p_aO_2/F_iO_2 ratio 55.7 ± 15.9 associated with a calculated transpulmonary shunt (Q_s/Q_t) of 0.52 ± 0.22 (n = 81), p_aCO_2 of 45.5 ± 12.8 mmHg, and pre-ECLS ventilator days 3.5 ± 2.7 days. Ventilator settings included an average peak inspiratory pressure (PIP) of 46.5 ± 13.4-cm water, PEEP of 13.9 ± 4.8, and F_iO_2 of 1.00. The average duration of ECLS was 285.3 hours (range, 20–1357 hours).

Six patients with hypercarbic respiratory failure had an average p_aCO_2 of 84.0 ± 31.5 mmHg and a pH of 7.19 ± 0.18. These patients had adequate oxygenation as shown by p_aO_2/F_iO_2 ratio. The average ventilator settings in these patients included a PIP of 51.3 ± 9.9-cm water, a PEEP of 2.2 ± 3.5-cm water. The average duration of ECLS was 54 hours (range, 14–117 hours).

Primary diagnoses and overall survival are outlined in Table 2. Forty-nine patients had pneumonia with bacterial (49%), and viral (45%), etiologies being the most predominant. The overall survival for this group was 53%. Forty-five were classified as ARDS due to trauma (43%), extrathoracic

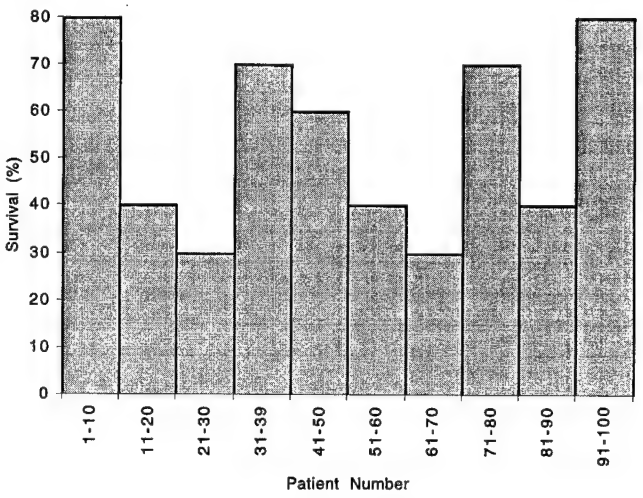

Figure 2. Percent survival by deciles of patients.

sepsis (16%), and a variety of other causes. The overall survival for ARDS was 51%. Overall survival of patients with hypoxemic respiratory failure was 52%.

Six patients had hypercarbic respiratory failure. Four of these cases were because of status asthmaticus unresponsive to maximal pharmacologic therapy, and two were because of acute tracheal obstruction by blood clot or charcoal. The overall survival in this group was 83%. The only nonsurvivor in this group was a patient with status asthmaticus who died of intracerebral bleeding related to acute hypertensive crisis.

Initially, we treated 5 to 10 patients per year, but we have treated between 20 and 25 patients per year in the past 3 years. Outcome by decile is shown in Figure 2. The cumulative survival in the first ten patients treated on the standardized protocol was 80%. After this experience, we accepted patients outside the initial contraindications, reflected in the range of survival shown in Figure 2. Survival in the last 30 patients is 63%.

Mode of Extracorporeal Life Support

The mode of access of ECLS is listed in Table 3. A total of 65 patients underwent VV ECLS, including 6 patients

Table 3. MODE OF ACCESS FOR ADULT RESPIRATORY ECLS

	n	Survival (%)
Venovenous	65	61.5
Venoarterial	11	27.3
Venoarterial changed to venovenous	11	81.8
Venovenous changed to venoarterial	7	0.0
Other*	6	33.3

ECLS = extracorporeal life support.
* Cases that included transition between venovenous and venoarterial modes of access more than once.

Table 4. MECHANICAL COMPLICATIONS DURING ADULT RESPIRATORY ECLS (N = 100)

Complication	%	% Survival
Oxygenator failure	32.0	40.6
Tubing rupture, circuit disruption	15.0	33.3
Pump failure	5.0	60.0
Heat exchanger malfunction	4.0	75.0
Clots in circuit	9.0	55.6
Air in circuit	3.0	33.3
Cannula removal, placement problems	5.0	60.0
Other	12.0	33.3

ECLS = extracorporeal life support.

with hypercarbic respiratory failure (survival 61.5%). Eleven patients underwent VA ECLS (survival 27.3%). An additional 11 patients initially were placed on VA ECLS and then converted to VV ECLS when hemodynamically stable (survival 81.8%). Seven patients, initially placed on VV ECLS, were converted to VA ECLS during their course of ECLS (survival 0%); four patients were connected to VA ECLS due to profound sepsis and three patients due to cardiac arrest. Six patients underwent more than one change in the mode of ECLS due to improvement or worsening of cardiovascular function during ECLS (*e.g.*, VV→VA→VV) (survival 33.3%).

Complications

There were a total of 479 complications (4.8 ± 3.1 per case), of which 85 were mechanical (0.9 ± 0.9 per case) and 394 were patient related (3.9 ± 2.7 per case). Incidence and percent survival for all reported mechanical and patient complications are outlined in Tables 4 and 5, respectively. Common mechanical problems included oxygenator failure (32 cases, 40.6% survival), tubing or circuit disruption (15 cases, 33.3% survival), and clots in the circuit (9 cases, 55.6% survival). No patient died of a mechanical complication. Patient-related complications included significant surgical site bleeding (69 cases, 33% survival) due to cannula site bleeding (30 cases) and other surgical site bleeding (39 cases), arrhythmias (30 cases, 33.3% survival), need for inotropes (52 cases, 40.4% survival), need for cardiopulmonary resuscitation (12 cases, 0% survival), new onset pneumothorax (24 cases, 41.7% survival), culture-proven infection (29 cases, 37.9% survival), elevated creatinine (53 cases, 30.2% survival), and need for hemofiltration (47 cases, 29.8% survival). In addition, there were six cases of clinical brain death or lack of cortical function, four cases of intracranial hemorrhage or infarct (0% survival), and six cases of a major gastrointestinal bleeding (0% survival). Four patients had no complications, and all survived.

Statistical Modeling of Predictors of Survival

Univariate data of survivors and nonsurvivors are listed in Tables 4 through 6. Stepwise logistic regression modeling was performed for the 94 patients with hypoxemic respiratory failure to establish both pre-ECLS variables and variables during ECLS that were independently associated with outcome survival. Diagnoses were not entered into either model. The complete model of pre-ECLS variables included the following: 1) A-aDO_2; 2) age; 3) p_aO_2/F_iO_2 ratio; 4) ventilator days; 5) transport on ECLS; 6) respiratory management (moribund *vs.* 12 hours, Univer-

Table 5. PHYSIOLOGIC COMPLICATIONS DURING ADULT RESPIRATORY ECLS (N = 100)

Complication	%	% Survival
Hemorrhagic		
Intracranial infarct	2.0	0.0
Intracranial hemorrhage	2.0	0.0
Gastrointestinal hemorrhage	6.0	0.0
Cannula site bleeding	30.0	33.3
Other surgical site bleeding	39.0	33.3
Hemolysis	8.0	37.5
Other	9.0	55.6
Cardiovascular		
CPR required	12.0	0.0
Arrhythmias	30.0	33.3
Inotropes	52.0	40.4
Hypertension	13.0	46.2
Other	3.0	33.3
Pulmonary		
Pneumothorax	24.0	41.7
Pulmonary hemorrhage	1.0	0.0
Other	7.0	57.1
Infectious		
Culture proven infection	29.0	37.9
WBCs < 1500	6.0	16.7
Neurologic		
Brain death/lack cortical function	6.0	0.0
Probable or definite seizure	4.0	50.0
Other	2.0	100.0
Renal		
Creatinine >1.5, <3.0 mg/dL	22.0	31.8
Creatinine >3.0 mg/dL	31.0	29.0
Dialysis	3.0	33.3
Hemofiltration	47.0	29.8
Hepatic		
Bilirubin >5.0 mg/dL	4.0	25.0
Elevated liver enzymes	3.0	33.0

ECLS = extracorporeal life support; CPR = cardiopulmonary resuscitation; WBCs = white blood cells.

Table 6. CHARACTERISTICS OF SURVIVORS AND NONSURVIVORS WHO UNDERWENT ECLS FOR SEVERE HYPOXEMIC RESPIRATORY FAILURE

	Survivors (n = 49)	Nonsurvivors (n = 45)
Male/female (%)	(51.0/49.0)	(42.2/57.8)
Age (yr)	31.6 ± 11.4	36.4 ± 13.3
Weight (kg)	77.1 ± 23.4	78.3 ± 21.1
Pre-ECLS		
p_aO_2/F_iO_2 ratio	59.8 ± 16.4	51.3 ± 14.4
p_aO_2 (mmHg)	59.3 ± 16.0	49.6 ± 11.9
p_aCO_2 (mmHg)	59.3 ± 16.0	46.4 ± 10.3
pH	7.35 ± 0.11	7.33 ± 0.11
Ventilator days	2.7 ± 2.1	4.4 ± 3.0
S_aO_2	84.1 ± 10.5	79.6 ± 13.1
S_vO_2	51.8 ± 22.3	47.5 ± 20.5
Duration of ECLS (hr)	213.7 ± 166.1	365.3 ± 300.2
Average number of mechanical complications/patient	0.7 ± 0.8	1.1 ± 1.0
Average number of patient complications/patient	2.5 ± 1.7	5.7 ± 2.6

ECLS = extracorporeal life support.

sity of Michigan protocol); 7) gender; 8) weight; 9) S_aO_2; 10) S_vO_2; and 11) Q_s/Q_t. The variables "S_vO_2" and "Q_s/Q_t" were excluded from the model because 13 patients did not have this measurement. The only pre-ECLS variables found to be independently predictive of outcome after stepwise logistic regression modeling were: 1) age; 2) p_aO_2/F_iO_2 ratio; and 3) pre-ECLS ventilator days (Table 7). Predicted probabilities of survival were calculated based on this model and are shown graphically in Figure 6. In general, older patients with severe hypoxemia who underwent prolonged pre-ECLS ventilator treatment had the poorest survival.

The complete model of variables during ECLS included those variables listed in Table 5 (mechanical complications) and Table 6 (physiologic complications) as well as the inclusion of age, hours on ECLS, gender, and weight. Several variables were always associated with mortality: cardiopulmonary resuscitation, intracranial infarct or hemorrhage, significant gastrointestinal bleeding, and the determination of clinical brain death. These conditions were not included in the model. The only remaining variables during ECLS that proved to be significantly associated with outcome were the presence of serum creatinine >1.5 mg/dL and significant surgical site bleeding as listed in Table 7. None of the mechanical complications were independent predictors of outcome survival.

The reasons for death are listed in Table 8. Extracorporeal life support was terminated for futility in 34 (74%) with the majority of these cases due to proven or presumptive pulmonary fibrosis (10 patients, 29%), poor neurologic status (11 patients, 32%), multiorgan system failure (7 patients, 21%), and septic shock (4 patients, 12%). Cardiac arrest from which the patient could not be resuscitated accounted for 12% of deaths during ECLS. Eight patients who recovered lung function sufficiently to wean from ECLS died in the hospital after the removal of the device a mean of 25.8 days (range, 6–94 days). Of these, two patient died directly due to lung-related complications, one patient with pulmonary fibrosis and one with intrapulmonary bleeding after necrotizing pneumonia.

All but 2 of the 54 survivors are leading normal, healthy lives. Some have a mild restrictive pattern on flow and volume testing, but none have chronic lung disease or limitation of activity. One patient required distal foot amputation for ischemia on the side of femoral venous can-

Table 7. SUMMARY OF THE STEPWISE LOGISTIC REGRESSION MODELS OF THE DEPENDENT VARIABLE "SURVIVAL" FOR 94 PATIENTS WITH PRIMARY HYPOXEMIC RESPIRATORY FAILURE TREATED WITH ECLS

Variable	β	SE	Chi Square	p Value	Odds Ratio
Pre-ECLS					
Age (yr)	>0.0580	0.0209	7.7005	0.0055	1.060
p_aO_2/F_iO_2 ratio	0.0628	0.0204	9.4636	0.0021	0.939
Ventilator days	−0.4607	0.1261	13.3422	0.0003	1.585
Constant	0.1962	1.2164	—	—	—
During ECLS					
Bleeding	−2.0247	0.5819	12.1080	0.0005	7.574
Creatinine >1.5 mg/dL	−2.6513	0.5805	20.8618	<0.0001	14.172
Constant	2.7127	0.6148	—	—	—

β = estimated coefficient for independent variables; SE = standard error; chi-square = maximum likelihood Wald test; constant = constant term in the model; ECLS = extracorporeal life support. Predicted probabilities of survival can be determined from the equation $Pr(\text{survival}) = 1/(1 + e^{-z})$, where $z = \beta_1 + \Sigma \beta_i X_i$, where β_1 is the constant term and β_i is the corresponding coefficient for variable X_i.

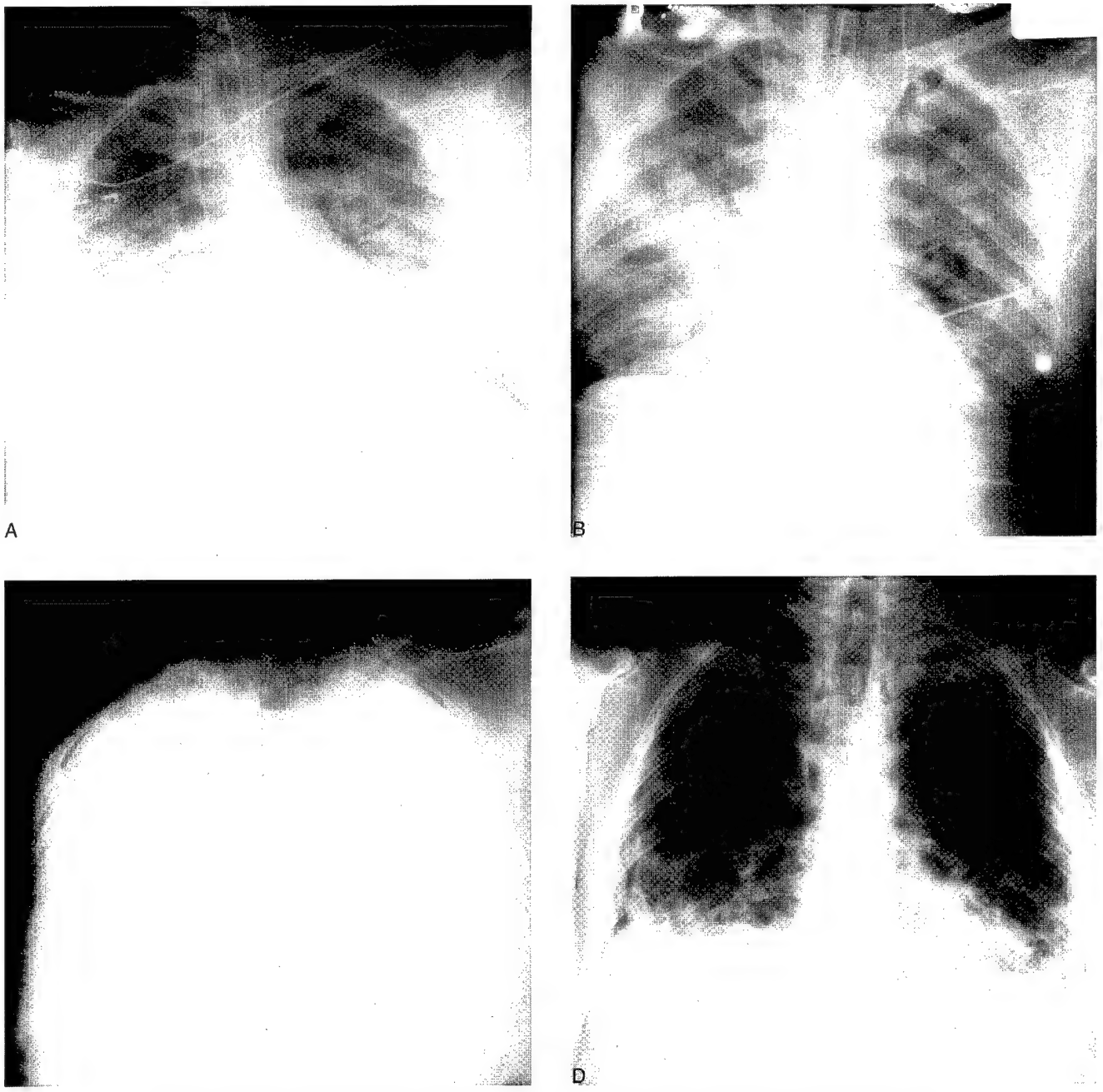

Figure 3. Chest radiographs of patient 1 (A) before the institution to extracorporeal life support (B) and just after the institution of venovenous extracorporeal life support. Note the position of the drainage cannula extending from the right internal jugular vein to the right atrium and (C) during the trial of partial liquid ventilation. The radiodense perfluorocarbon outlines the contour of the lungs (D) at the time of discharge from the hospital.

nulation, and one patient had a pseudoaneurysm of the femoral artery develop. Two patients became deaf, and one has mild memory limitation from pre-ECLS cardiac arrest. Several patients had profound weakness, which recovered completely. One of the patients with deafness and weakness died suddenly 2 years after discharge. One other patient died of complications of multiple enteric fistulas 1 year after discharge.

Illustrative Case Reports

Patient 1

The patient was a 36-year-old man who had Legionella pneumonia and ARDS. After 5 days of mechanical ventilation, he had multiorgan system failure with renal failure, jaundice, sepsis syndrome, and was referred for ECLS. Ventilator settings before ECLS were tidal volume

Table 8. REASON FOR DEATH IN PATIENTS WHO UNDERWENT ECLS FOR SEVERE RESPIRATORY FAILURE

Reason	Number
Futility	34
Poor neurologic status	10
Intracranial infarct/hemorrhage	4
Brain death/lack cortical function	6
Pulmonary fibrosis or nonfunction*	10
Multiple organ system failure	8
Septic shock	4
Intrapulmonary hemorrhage	1
Bowel infarction	1
Cardiac arrest	4
Late death (post-ECLS)	8
Septic shock	2
Multiple organ failure syndrome	1
Intracranial hemorrhage	2
Pulmonary embolus	1
Intrapulmonary hemorrhage	1
Pulmonary fibrosis*	1
Total	46

ECLS = extracorporeal life support.
* Biopsy proven pulmonary fibrosis or presumptively diagnosed based on minimal lung function and mean pulmonary artery pressure/mean systemic artery pressure (MPAP/MAP) > 0.67.

780 mL, respiratory rate 21/minute, PIP 35-cm water, PEEP 10-cm water, F_iO_2 1.0 with an arterial blood gas pH 7.25, pO_2 79, pCO_2 47, and O_2 saturation 93%. The p_aO_2/F_iO_2 ratio was 79. The patient's initial chest radiograph before ECLS is shown in Figure 3A. The patient was unstable at the time of transfer and required ECLS. The patient was receiving VV ECLS for 257 hours as shown in Figure 3B. He was entered into a clinical trial of partial liquid ventilation during ECLS for the first 5 days as shown in Figure 3C. Multiorgan system failure persisted and renal failure was treated with hemofiltration. Bilirubin reached 25 mg/dL. He was comatose for 5 days. The patient successfully was weaned from ECLS to conventional ventilation for another 12 days. He spent a total of 15 days in the ICU post-ECLS and was discharged on hospital day 40. All organs recovered. His chest radiograph at the time of discharge from hospital is shown in Figure 3D.

Patient 2

The patient was a 23-year-old woman with a history of thrombotic thrombocytopenic purpura, status postsplenectomy who had the following diagnoses: streptococcal pneumonia and septicemia, purpura fulminans, consumptive coagulopathy, sepsis. She was referred for ECLS on the third day of mechanical ventilation. She did not improve after 24 hours on our optimal management protocol. Before ECLS, the patient had renal failure and elevated liver enzymes and required inotropes for cardiovascular support. Her ventilator settings just before ECLS were respiratory rate 20, PIP 56-cm water, PEEP 10-cm water, F_iO_2 1.0 with arterial blood gas pH 7.11, pO_2 40, pCO_2 69, O_2 saturation 48%. The p_aO_2/F_iO_2 ratio was 40. The patient's chest radiograph just before the institution of ECLS is shown in Figure 4A.

The patient required VV ECLS as shown in Figure 4B. She required two runs of ECLS. On ECLS day 5, lung function improved and ECLS was stopped. However, respiratory function deteriorated over the next 12 hours and VV ECLS was reinstituted for 6 more days. The patient's course was complicated by liver failure (bilirubin 6 mg/dL); renal failure requiring hemofiltration; multiple positive blood; sputum and urine cultures; purpura, which sloughed and ultimately required split-thickness skin grafting of 20% of the body surface area; and coma. The patient required 52 post-ECLS ventilator days and 57 post-ECLS ICU days. All organ functions returned to normal. She was discharged from the hospital on the 113th hospital day (Fig. 4C).

Extracorporeal life support treated septic shock and multiorgan system failure. Coma was ominous (lowest Glasgow coma score was <5 for several days), but all organs recovered when the lungs recovered.

Patient 3

The patient was a 28-year-old woman in whom necrotizing pancreatitis developed due to alcohol abuse. She was intubated for respiratory failure and underwent pancreatic debridement. After surgery, the patient had progressive respiratory failure. After 7 days of mechanical ventilation, she was referred for ECLS. Her ventilator settings before ECLS were respiratory rate 12, PIP 40-cm water, PEEP 16-cm water, F_iO_2 1.0 with arterial blood gas 7.45 pO_2 67 mmHg, $pCO_2$66 mmHg, O_2 saturation 91%. The p_aO_2/F_iO_2 ratio was 67. The chest radiograph just before ECLS is shown in Figure 5A. The patient required VV ECLS for 177 hours (Fig. 5B). The patient's course was complicated by renal failure, development of abdominal abscesses, and sepsis. In addition, the patient underwent exploratory laparotomy with pancreatic debridement four times without complication while receiving ECLS. On ECLS day 7, the patient was weaned from ECLS. She required an additional 13 post-ECLS ventilator days and 24 post-ECLS ICU days. All organs returned to normal, and she was discharged on the 75th hospital day (Fig. 5C).

DISCUSSION

Extracorporeal life support is standard therapy for neonatal respiratory failure and is gaining wider acceptance for pediatric respiratory failure. In >15,000 patients compiled in the Extracorporeal Life Support Organization registry,[1] survival among neonates undergoing ECLS for respiratory failure is 80% and approaches 90% among the most experienced ECLS centers. In a recent prospective, controlled, randomized trial of ECLS in neonatal respiratory failure in the United Kingdom, survival in the ECLS

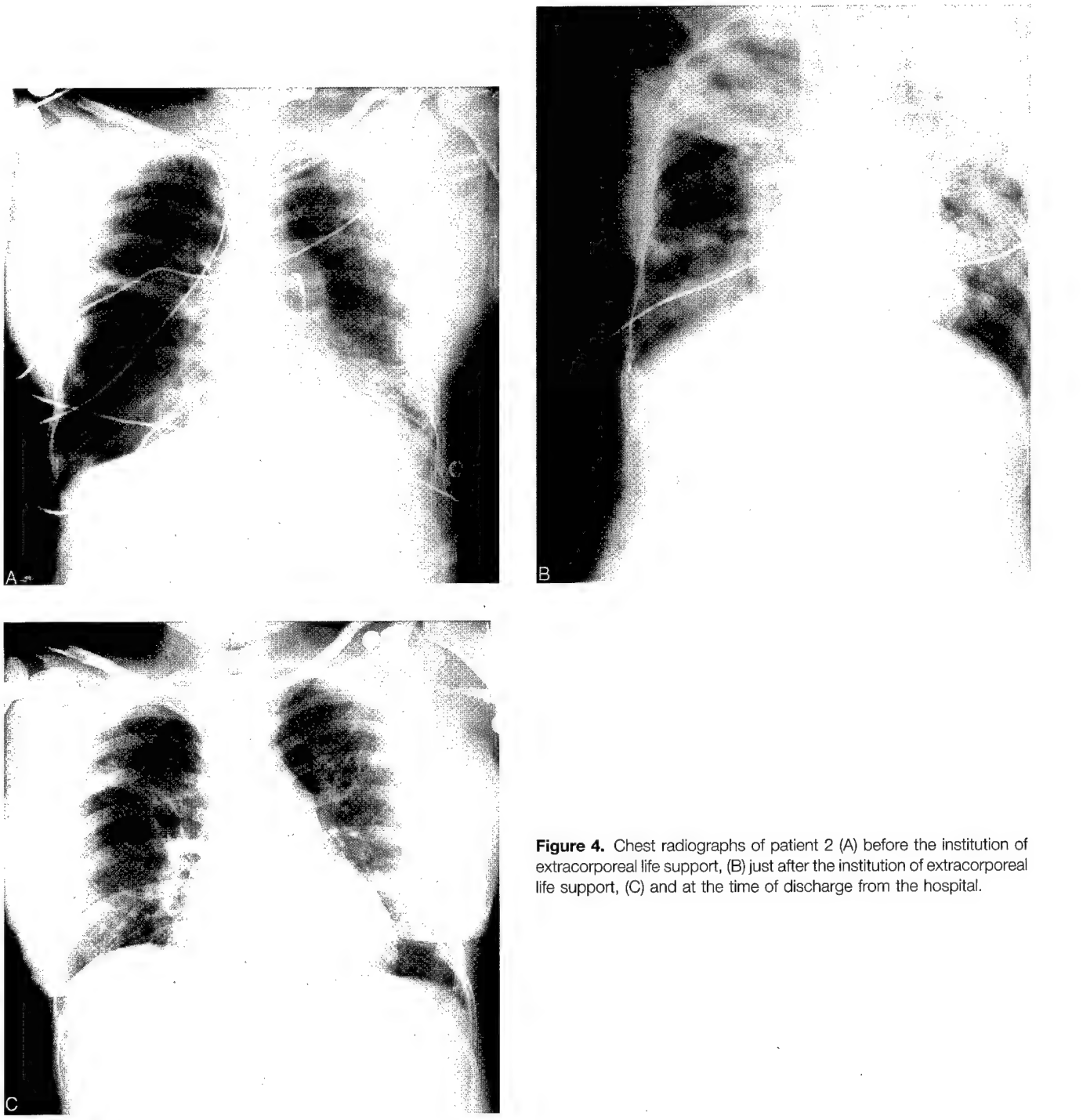

Figure 4. Chest radiographs of patient 2 (A) before the institution of extracorporeal life support, (B) just after the institution of extracorporeal life support, (C) and at the time of discharge from the hospital.

group was 72% and 40% in the control group. Based on this study, the National Health Service established ECLS as standard treatment for severe neonatal respiratory failure in the United Kingdom.[32] In a multicenter review of 331 pediatric patients with respiratory failure in 1991, the only treatment measure correlated with survival was ECLS.[33] When these same patients were further analyzed by double-matched pairs, patients who received ECLS showed a significantly improved survival over conventionally treated patients (73% *vs.* 53%, respectively).[2] From this large experience in neonates and children, ECLS has been shown to be effective in patients with reversible severe respiratory disease. In 1990, we began a standardized protocol for the management of severe adult respiratory failure, emphasizing protecting the lung from high-pressure, high-oxygen injury, which included

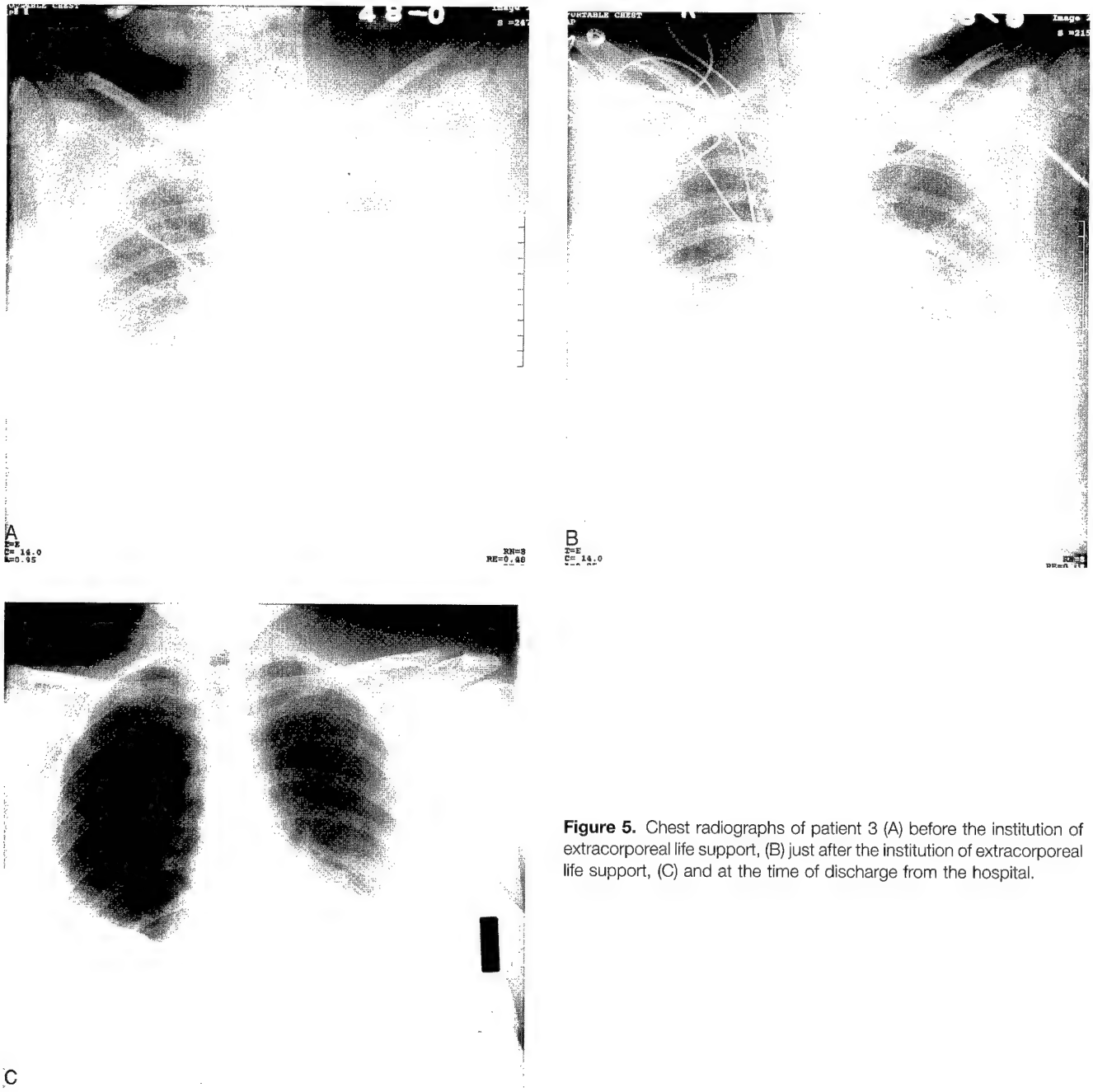

Figure 5. Chest radiographs of patient 3 (A) before the institution of extracorporeal life support, (B) just after the institution of extracorporeal life support, (C) and at the time of discharge from the hospital.

ECLS if the patient did not respond to conventional treatment. Extracorporeal life support is treatment for the patient, but is not a therapy to treat diseased lungs. It is a life-support system that allows injured lungs the best chance to heal as well as to allow other therapies to be evaluated (*e.g.,* partial liquid ventilation).[34,35] Ultimately, even with flawless implementation of ECLS, the lung's capacity to heal determines survival outcome.

In our study, 141 patients entered into our protocol over 6 years; 62% recovered and survived. All were referred from other ICU services. One hundred underwent ECLS and 54% survived to hospital discharge. Other experienced centers in Europe have reported similar experiences with 50% to 66% survival (Lewandowski et al.,[9] 32 cases, 53% survival; Lennartz et al.,[36] 182 cases, 58% survival; Peek and Firmin,[37] 50 cases, 66% survival; Brunet et al.,[8] 23 cases, 50% survival; Pesenti et al.,[38] 87 cases, 46% survival) with similar severity of respiratory failure as judged by p_aO_2/F_iO_2 ratio, transpulmonary shunt, and compliance compared to our group of patients.

Our multivariate logistic regression analyses of 94 adult patients who received ECLS for severe hypoxemic respi-

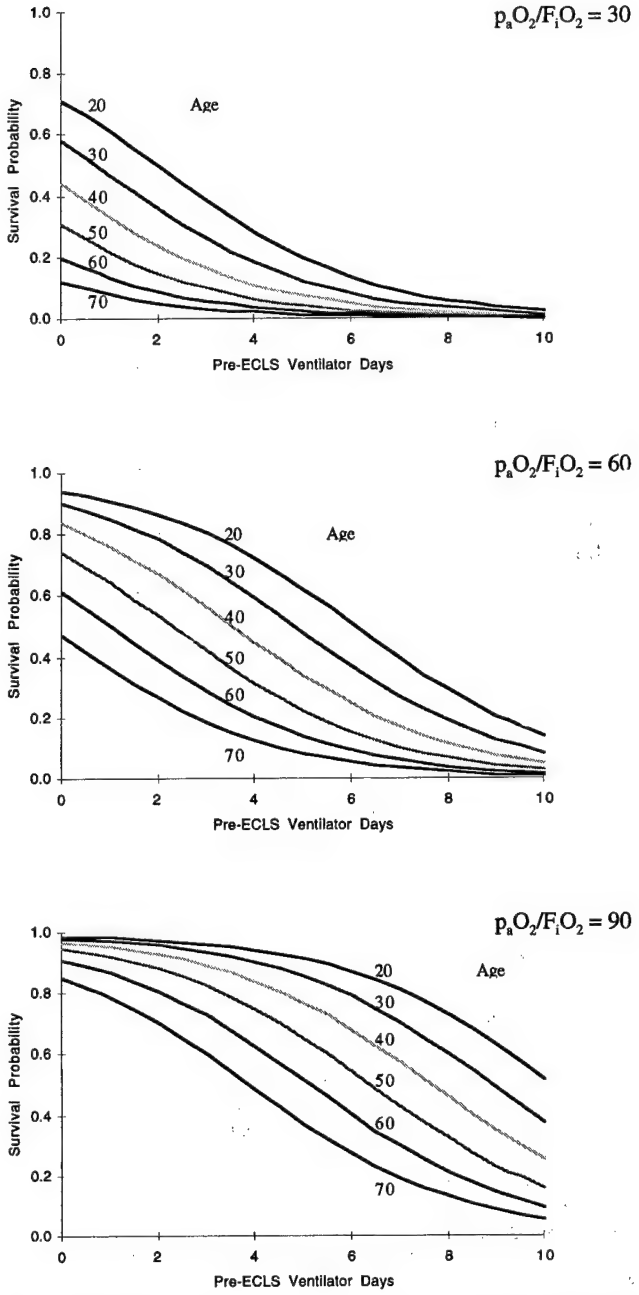

Figure 6. Graphical representation of the effect of pre-extracorporeal life support ventilator days and age on probability of survival shown for three p_aO_2/F_iO_2 ratios as derived from the multiple logistic regression model of pre-extracorporeal life support variables. Each curve represents a given age in years as labeled.

ratory show several important outcome associations that may be important for improved survival predictability and for establishing entry and exclusion criteria for future prospective ECLS trials. Pre-ECLS predictors of outcome survival or mortality were age, p_aO_2/F_iO_2 ratio, and pre-ECLS ventilator days. Patients with longer duration of mechanical ventilation before the institution of ECLS had poorer outcomes. This may be related to ventilator-induced injury superimposed on previously injured lung. Studies based on animal data have shown that irreversible lung injury is promoted during mechanical ventilation by continued barotrauma,[39] volutrauma,[40] and oxygen toxicity.[41] A limitation of this analysis, however, is that it does not provide distinction of the level of ventilator pressures or F_iO_2 during the course of ventilation before ECLS.[42] Often, the ventilator course was not uniform but was considered optimal by referral physicians.

Of the variables during ECLS associated with outcome, no mechanical complications were independent predictors of survival, suggesting that the devices were safe and reliable with weeks of continued use. The physiologic variables associated with outcome were brain injury, cardiac arrest, bleeding, and creatinine >1.5 mg/dL. Sixty-eight percent of our patients had significant bleeding either from the site of cannulation or from another surgical site. Although control of coagulation has improved, significant bleeding remains a problem. The advent of new bioartificial surface coatings and strategies, such as the use of nitric oxide in the oxygenator ventilating gas,[43] shows promise in alleviating this complication. Fifty-two patients had creatinine >1.5 mg/dL and more than half of these patients had creatinine >3 mg/dL. The etiology of renal failure is a manifestation of multiple organ system failure.

Six patients were treated for status asthmaticus or airway obstruction. In these patients, oxygenation was more than adequate with the primary problem being hypercarbia associated with high intrathoracic pressures, cardiovascular collapse, or barotrauma. In these patients, low-flow ECLS was used for carbon dioxide removal and permitted decreased ventilator settings to low nondamaging settings, allowing therapeutic interventions to be instituted directly to the airway. Although these are not problems of parenchymal lung disease, these conditions generally respond promptly and are therefore ideally managed with ECLS.

Forty-nine (52%) patients who had *hypoxemic respiratory failure* were discharged, and all but two are leading healthy lives. Does this represent major salvage from certain mortality or minor improvement on conventional care? These patients were referred from ICUs *despite and after* 1 to 10 days of conventional care, which was viewed as optimal in those units. Thirty of these patients could not be transported on a ventilator and received ECLS in the referral hospital and transported back to our hospital. Thirty-nine other patients received ECLS on arrival in our ICU because of moribund status. There is no comparable group of patients reported in the literature to define the mortality risk of patients with cardiorespiratory failure too unstable to transport or failing on maximal conventional care. In our series, 39 (57%) of these 69 patients survived. Sixty-six patients with hypoxemia were stable enough on arrival to our ICU to be treated with our opti-

mal care protocol. This group is comparable to the 51 patients who met "ECMO criteria" at LDS hospital (Salt Lake City, UT) reported by Suchyta and Morris in 1991[26] and comparable to the overlapping 40 patients in the LDS hospital randomized $ECCO_2R$ study (1994).[7] Forty-two percent of the patients in this study survived on a tightly controlled ventilator management protocol. Sixty-six percent of our comparable patients survived. Forty-one of these patients improved with our optimal care protocol (34 survived). Twenty-five did not and were treated with ECLS; 10 (40%) of these survived.

There are other reports in the literature of "severe respiratory failure," which usually is defined as classic ARDS criteria[22,24] with Murray lung injury[28] score >2.5 and p_aO_2/F_iO_2 ratio <70 to 80.[25,27] It is not possible to compare our series directly to these reports, because the Murray score and p_aO_2/F_iO_2 ratio reported is the worst-case measurement usually on the first day of treatment, whereas our scoring is the best possible measurement despite and after days of optimal treatment. Several reports document increasing mortality in ARF with each day that goes by without significant improvement.[44] Our patients arrived after 3.5 days (average) of mechanical ventilation. Despite these limitations, the 52% survival for the hypoxemic ECLS patients is considerably better than that reported for ARF in other series,[7,24,26,27,30,31] with the single exception of the report of Hickling et al.,[25] who reported 22% mortality for ARF (based on the first day, worst-case p_aO_2/F_iO_2 ratio).

With only six patients in the hypercarbic group, it is difficult to know what the outcome would have been without ECLS. The two patients with airway obstruction could not be bronchoscoped without ECLS and would have died. Status asthmaticus of several days' duration despite maximal therapy has a high mortality risk.

We believe that at least 80 to 90 of these 100 patients would have died without extracorporeal support because:

1. These patients were referred after not responding to best conventional therapy in other ICUs.
2. All patients with hypoxemia went through a phase of ECLS when the native lung gas exchange was insufficient to support life and the Murray score was 4.
3. Thirty-five percent of the patients required ECLS for transfer to our hospital.
4. Of the patients treated in our ICU, ECLS was used only for the patients who did not improve (comparable to the control group patients in the Morris study who died).

However, the only way to determine the effectiveness of ECLS in ARF is to conduct a prospective, comparative study. Two prospective, randomized trials have been carried out in adult respiratory failure. The first conducted from 1975 to 1979 showed only 10% survival in both conventional and ECMO groups.[5] The technology of all aspects of management has changed considerably since that study. The prospective, randomized comparison of $ECCO_2R$ and conventional management conducted by Morris et al.[7] showed 42% survival with protocol ventilator care and 33% with $ECCO_2R$. Extracorporeal CO_2 removal as practiced in that study included low blood flow inadequate to provide full oxygenation support, major bleeding complications, and no on-ECLS transport. The techniques and results of ECLS have improved in recent years. Vascular access and blood flow are planned to provide total oxygen and CO_2 support. Bleeding still is a significant complication but rarely a life-threatening problem. Instituting ECLS in the referral hospital is necessary in a third of our cases. Experienced centers report 49% to 66% survival in patients with high risk of mortality. A new prospective study of treatment for severe ARF should be done, comparing a complete protocol including ECLS to other protocols. While such a study is being implemented, we consider ECLS to be a reasonable treatment for patients with ARF unresponsive to other methods of treatment.

In conclusion, ECLS provides life support in ARF in adults, allowing time for injured lungs to recover. In 100 patients selected for high mortality risk despite and after optimal conventional treatment, 54% survived. Extracorporeal life support is extraordinary, but reasonable, treatment in severe adult respiratory failure. Predictors of survival exist that may be useful for patient prognostication and future prospective studies.

Acknowledgments

The authors thank the many members of the staff of the University of Michigan Medical Center who participated in the care of these patients, the survival flight transport team, the surgical intensive care unit staff, the operating room staff, and the blood bank staff, all of whom were essential in the treatment of these patients. The authors also thank the ECLS team, headed by Robin Chapman, R.N., which is a highly specialized and uniquely dedicated group of individuals who carry the major responsibility for these patients. Physicians who cared for these patients include: Drs. Harry L. Anderson, Jr, James Sinard, Ralph Delius, Michael Shapiro, Charles Shanley, Kenneth McCurry, Cynthia Steimle, Joan VanCamp, Richard Tooley, Thomas Pranikoff, David Bliss, Franco Fazzalari, Philip Bongiorno, Dorothy Lewis, Paul Gauger, Vania Orfanou, Craig Reickert, W. Anthony Lee, Andrew Michaels, and John Younger.

References

1. ECMO Quarterly Report (January). ECMO Registry of the Extracorporeal Life Support Organization (ELSO), 1997.
2. Green TP, Timmons OT, Fackler JC, et al. The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Crit Care Med 1996; 24:323–329.
3. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome): use of the Branson membrane lung. N Engl J Med 1972; 286:629–634.

4. Bartlett RH, Gazzaniga AB. Extracorporeal circulation for cardiopulmonary failure. Curr Probl Surg 1978; 15.
5. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe respiratory failure. JAMA 1979; 242:2193–2196.
6. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive pressure ventilation with extracorporeal CO2 Removal in severe acute respiratory failure. JAMA 1986; 256:881–886.
7. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; 149:295–305.
8. Brunet F, Belghith M, Mira J, et al. Extracorporeal carbon dioxide removal and low-frequency positive-pressure ventilation: improvement in arterial oxygenation with reduction of risk of pulmonary barotrauma in patients with adult respiratory distress syndrome. Chest 1993; 104:889–898.
9. Lewandowski K, Lewandowski M, Papper D, Falke KJ. Outcome and follow-up of adults following extracorporeal life support. In: Zwischenberger J, Bartlett RH, eds. ECMO: extracorporeal cardiopulmonary support in critical care: Extracorporeal Life Support Organization, 1995.
10. Brunet F, Mira J, Makhlouf B, et al. Extracorporeal carbon dioxide removal technique improves oxygenation without causing overinflation. Am J Respir Crit Care Med 1994; 149:1557–1562.
11. Manert W, Haller M, Briegel J, et al. Venovenous extracorporeal membrane oxygenation (ECMO) with a heparin-lock bypass system: an effective addition in the treatment of acute respiratory failure (ARDS). Anaesthetist 1996; 45:438–448.
12. Shanley CJ, Hirschl RB, Schumacher RE, et al. Extracorporeal life support for neonatal respiratory failure: a 20-year experience. Ann Surg 1994; 220:269–282.
13. Moler FW, Custer JR, Bartlett RH, et al. Extracorporeal life support for pediatric respiratory failure. Crit Care Med 1992; 20:1112–1118.
14. Anderson HL, III, Delius RE, Sinard JM, et al. Early experience with adult ECMO in the modern era. Ann Thorac Surg 1992; 53:553–563.
15. Anderson H, III, Steimle C, Shapiro M, et al. Extracorporeal life support for adult cardiorespiratory failure. Surgery 1993; 114:161–172.
16. Shapiro MB, Kleaveland AC, Bartlett RH. Extracorporeal life Support for status asthmaticus. Chest 1993; 103:1651–1654.
17. Pranikoff T, Hirschl RB, Steimle CN, et al. Efficacy of extracorporeal life support in the setting of adult cardiorespiratory failure. ASAIO J 1994; 40:M339–M343.
18. Kolla S, Lee WA, Hirschl RB, Bartlett RH. Extracorporeal life support for cardiovascular support in adults. ASAIO J 1996; 42:M809–M819.
19. Bartlett RH. Critical care physiology. Boston: Little Brown and Co, 1995.
20. Shanley CJ, Bartlett RH. The management of acute respiratory failure. Curr Opin Gen Surg 1994:7–16.
21. Bartlett RH. Management of ECLS in adult respiratory failure. In: Zwischenberger J, Bartlett RH, eds. ECMO: extracorporeal cardiopulmonary support in critical care: Extracorporeal Life Support Organization, 1995.
22. Bernard GR, Artigas A, Brigham KL, et al. The American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 1994; 149:818–824.
23. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet 1967; 2:319–323.
24. Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury: predictors of mortality. Am J Respir Crit Care Med 1995; 152:1818–1824.
25. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. Intensive Care Med 1990; 16:372–377.
26. Suchyta MR, Clemmer TP, Orme JF, et al. Increased survival of ARDS patient with severe hypoxemia (ECMO criteria). Chest 1991; 99:951–955.
27. Vasilyev S, Schaap RN, Mortensen JD. Hospital survival rates of patients with acute respiratory failure in modern respiratory care units: an internation, multicenter, prospective survey. Chest 1995; 107:1083–1088.
28. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; 138:720–723.
29. Bartlett RH, Morris AH, Fairley HB, et al. A prospective study of acute hypoxic respiratory failure. Chest 1986; 89:684–689.
30. Morel DR, Dargent F, Bachmann M, et al. Pulmonary extraction of serotonin and propranolol in patients with adult respiratory distress syndrome. Am Rev Respir Dis 1985; 132:479–484.
31. Zapol WM, Firkker MJ, Pontoppidan H, et al. The adult respiratory distress syndrome at Massachusetts General Hospital: etiology, progression, and survival rate 1978–1988. In: Zapol WM, Lemare F, eds. Adult Respiratory Distress Syndrome. New York: Marcel Dekker, 1991.
32. UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. Lancet 1996; 348:75.
33. Timmons OD, Dean JM, Vernon DD. Mortality rates and prognostic variables in children with adult respiratory distress syndrome. J Pediatr 1991; 119:896–899.
34. Hirschl RB, Pranikoff T, Gauger P, et al. Liquid ventilation in adults, children, and full-term neonates. Lancet 1995; 346:1201–1202.
35. Hirschl RB, Pranikoff T, Wise C, et al. Initial experience with partial liquid ventilation in adult patients with acute respiratory distress syndrome. JAMA 1996; 275:383–389.
36. Lennartz H. Extracorporeal lung assist in ARDS: history and state of the art. Acta Anaethesiol Scand Suppl 1996; 109:114–116.
37. Peek GJ, Firmin RK. Extracorporeal membrane oxygenation, a favourable outcome? Br J Anaesth 1997; 78:235–236.
38. Pesenti A, Gattinoni L, Bombino M. Longterm extracorporeal support: 20 years of progress. Intensive & Critical Care Digest 1993; 12:15–18.
39. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation: an experimental study. Am Rev Respir Dis 1987; 135:312–315.
40. Dreyfuss D, Soler P, Basset G, et al. High inflation pressure pulmonary edema. Respective effects of high airway pressure. Am Rev Respir Dis 1988; 137:1159–1164.
41. Barber RE, Lee J, Hamilton WK. Oxygen toxicity in man, a prospective study in patients with irreversible brain damage. N Engl J Med 1970; 283:1479–1484.
42. Pranikoff T, Hirschl RB, Steimle CN, et al. Mortality is directly related to the duration of mechanical ventilation before the initiation of extracorporeal life support for severe respiratory failure. Crit Care Med 1997; 25:28–32.
43. Mellgren K, Friberg LG, Mellgren G, et al. Nitric oxide in the oxygenator sweep gas reduces platelet activation during experimental perfusion. Ann Thorac Surg 1996; 61:1194–1198.
44. Bone RC, Balk R, Slotman G, et al. Adult respiratory distress syndrome: sequence and importance of multiple organ failure. Chest 1992; 320:320–326.

Appendix 1. DETAILED SUMMARY OF PATIENTS TREATED WITH ECLS AT THE UNIVERSITY OF MICHIGAN MEDICAL CENTER, 1988–1996

Patient Number	Age (yr)	Sex	Diagnoses	Respiratory Classification	Other Classification	P/F Ratio	Pre-ECLS Ventilator Days	Respiratory Management (hr)	Transport	On ECLS (date)	Mode of ECLS	Duration of ECLS (hr)	Survived
1*	17	F	Multiple trauma, pulmonary contusion, closed head injury, status post splenectomy	ARDS	Trauma	43	18	Moribund	No	9/7/88	VV	314	No
2*	36	F	Pneumonia, postoperative CABG, coronary artery disease	Pneumonia (b)	ARDS	49	6	>12	No	9/23/88	VV	17	No
3*	25	F	Wilson's disease, liver failure	ARDS	Transplant	34	1	Moribund	No	3/21/89	VA	90	No
4	29	M	Necrotizing pancreatitis, ARDS	ARDS	Pancreatitis	77	0.5	>12	No	5/31/90	VA	75	Yes
5	22	M	Status post motor vehicle accident, femur fracture, closed head injury, h/o seizure disorder	ARDS	Trauma	52	0.5	Moribund	Yes	6/28/90	VV	50	Yes
6	35	M	Status post motor vehicle accident, crush injury to left chest resulting in flail chest and requiring left lower lobe wedge resection; respiratory failure status post thoracotomy and tracheostomy	ARDS	Trauma	48	1	Moribund	Yes	7/6/90	VA → VV	139	Yes
7	23	M	Sickle cell disease, viral pneumonia	Pneumonia (v)	ARDS	60	5	Moribund	Yes	8/13/90	VV → VA → VV	576	Yes
8	53	F	Bacterial (legionella) pneumonia, sepsis, bronchopleural fistula	Pneumonia (b)	ARDS	75	5	>12	No	8/27/90	VA → VV	240	No
9	27	F	Viral pneumonia	Pneumonia (v)	ARDS	63	4	>12	No	11/16/90	VV	124	Yes
10	41	M	Cytomegalovirus pneumonia status post left lung orthotopic transplant (4 wk)	Pneumonia (v)	Transplant, ARDS	64	2	>12	No	12/20/90	VA → VV	228	Yes
11	20	F	ARDS, sepsis, postpartum, cesearean section, nosocomial pneumonia	ARDS	Sepsis	58	3	Moribund	Yes	2/5/91	VA → VV	198	Yes
12	55	M	Bacterial (legionella) pneumonia; nosocomial pneumonia (*E. coli*)	Pneumonia (b)	ARDS	44	3	>12	No	2/28/91	VV	639	No
13	29	F	Viral pneumonia	Pneumonia (v)	ARDS	70	2	Moribund	Yes	4/27/91	VA → VV	131	Yes
14	48	F	Bacterial pneumonia, status post right orthotopic lung transplant	Pneumonia (b)	Transplant, ARDS	64	5	>12	No	7/15/91	VV	403	No
15	27	F	Aspiration pneumonitis, insulin dependent diabetes	Aspiration pneumonia	ARDS	95	8.5	>12	No	8/4/91	VV	419	No
16	23	F	Viral pneumonia	Pneumonia (v)	ARDS	32	7	>12	No	8/19/91	VA → VV	1246	No
17	22	F	Multiple trauma (ruptured bladder, liver laceration, fractured spleen, fractured pelvis) status post motor vehicle accident, postoperative ARDS, status post splenectomy and repair of liver and bladder lacerations	ARDS	Trauma	34	1	Moribund	Yes	12/16/91	VA	245	Yes
18	25	F	Bacterial pneumonia	Pneumonia (b)	ARDS	59	8	>12	No	1/8/92	VV	372	No
19	41	M	Bronchiolitis obliterans (BOOP)	ARDS	BOOP	43	4	>12	No	1/7/92	VV → VA → VV	379	No
20	42	M	Bacterial (legionella) pneumonia	Pneumonia (b)	ARDS	50	4	>12	No	3/3/92	VV	138	Yes
21	33	F	Status asthmaticus	Airway support	Asthma	414	1	Moribund	Yes	3/21/92	VV	22	Yes
22	20	F	Multiple fractures status post motor vehicle accident, pulmonary contusion	ARDS	Trauma	80	7	Moribund	Yes	5/16/92	VA → VV	394	Yes

(continues)

Appendix 1 (*continued*).

Patient Number	Age (yr)	Sex	Diagnoses	Respiratory Classification	Other Classification	P/F Ratio	Pre-ECLS Ventilator Days	Respiratory Management (hr)	Transport	On ECLS (date)	Mode of ECLS	Duration of ECLS (hr)	Survived
23	22	F	Respiratory failure probable viral pneumonia	Pneumonia (v)	ARDS	45	8	Moribund	No	6/2/92	VV	1083	No
24	24	M	Gunshot wound to left chest sustaining splenic injury and diaphragmatic injury, status post partial splenectomy, primary repair of the diaphragm, postoperative sepsis, aspiration pneumonitis	ARDS	Trauma	50	7	>12	No	8/5/92	VV	333	No
25	34	F	Status post motor vehicle accident with multiple trauma including pelvic fracture, bladder laceration, right popliteal artery injury	ARDS	Trauma	36	12	Moribund	No	8/10/92	VV	91	No
26	21	M	Bacteroides empyema, lung abscess, pneumothorax, status post left lower lobe lobectomy and decortication; status post motor vehicle accident with injuries including multiple left rib fractures, left pulmonary contusion 2–3 mo prior	Pneumonia (b)	Trauma, ARDS	51	8	Moribund	No	8/21/92	VV	600	Yes
27	19	M	Status post motor vehicle accident, femur fracture, liver laceration, pelvic fracture, bilateral pulmonary contusion, status post exploratory laparotomy for hemoperitoneum	ARDS	Trauma	44	6	>12	No	12/2/92	VV → VA	285	No
28	32	M	Status post stab wound to neck	ARDS	Trauma	35	11	>12	No	12/1/92	VV → VA	378	No
29	54	M	Airway obstruction clot, status post orthotopic liver transplant	Airway support	Transplant	51	12	Moribund	No	12/4/92	VV	21	Yes
30	17	F	Status post gunshot wound to the right hemithorax, status post exploratory thoracotomy and wedge resection of the right lower lobe	ARDS	Trauma	46	8	>12	No	12/27/92	VV	94	No
31	51	F	Primary pulmonary hypertension, status post right orthotopic lung transplant	ARDS	Transplant	46	1	Moribund	No	2/9/93	VA	272	No
32	47	F	Multiple trauma status post motor vehicle accident, aspiration	ARDS	Trauma	58	1	>12	No	2/22/93	VV	142	Yes
33	38	F	*Staphylococcus pneumonia,* toxic shock syndrome	Pneumonia (b)	ARDS	38	1	Moribund	No	2/26/93	VV → VA	163	No
34	35	F	Streptococcal pneumonia, pneumothorax, bronchopleural fistula, left empyema, chronic pancreatitis	Pneumonia (b)	ARDS	64	10	Moribund	Yes	5/18/93	VA → VV → VA → VV	735	Yes
35	21	F	Fat embolism, femur fracture, tibial plateau fracture status post motor vehicle accident	ARDS	Trauma	53	1	Moribund	Yes	6/17/93	VA	111	Yes
36	20	M	Viral pneumonia	Pneumonia (v)	ARDS	69	4	Moribund	No	7/7/93	VV	337	Yes
37	32	F	Postpartum liver failure, status post orthotopic liver transplant	ARDS	Transplant	59	5	Moribund	No	8/1/93	VV	66	Yes
38	242	M	Viral pneumonia	Pneumonia (v)	ARDS	39	2	Moribund	No	8/20/93	VV	72	Yes
39	22	F	Status post gunshot wound to abdomen	ARDS	Trauma	56	4	Moribund	No	8/22/93	VV	144	Yes

(*continues*)

Appendix 1 (*continued*).

Patient Number	Age (yr)	Sex	Diagnoses	Respiratory Classification	Other Classification	P/F Ratio	Pre-ECLS Ventilator Days	Respiratory Management (hr)	Transport	On ECLS (date)	Mode of ECLS	Duration of ECLS (hr)	Survived
40	57	F	Meningococcemia, sepsis	ARDS	Sepsis	38	1	Moribund	Yes	9/29/93	VA	152	No
41	37	M	Pneumococcal pneumonia, sepsis	Pneumonia (b)	ARDS	45	5.5	Moribund	Yes	10/28/93	VA	211	No
42	29	M	Status post gunshot wound to abdomen and buttocks, status post exploratory laparotomy	ARDS	Trauma	42	3	Moribund	No	11/1/93	VV	75	No
43	22	F	Peripartum bacterial (pneumococcal) pneumonia, left empyema and bronchopleural fistula, sepsis	Pneumonia (b)	ARDS	58	2	>12	No	11/19/93	VV	122	Yes
44	48	F	Severe pulmonary edema status post bilateral orthotopic lung transplant (underlying α_1-antitrypsin deficiency), unable to wean from cardiopulmonary bypass, hypotension	ARDS	Transplant	40	0	Moribund	No	12/2/93	VA	173	No
45	18	M	Viral pneumonia, sepsis	Pneumonia (v)	ARDS	45	2	Moribund	No	12/15/93	VV	85	Yes
46	29	F	Status post tricuspid valve replacement for tricuspid valve endocarditis, consumptive coagulopathy, staphylococcal sepsis	ARDS	Sepsis	34	3	Moribund	No	12/23/93	VA	213	No
47	57	M	Pulmonary edema status postendoscopic sinus surgery, negative pressure edema	ARDS	Negative pressure edema	35	1	Moribund	Yes	1/8/94	VV	85	Yes
48	38	F	Viral pneumonia (varicella zoster)	Pneumonia (v)	ARDS	56	1	Moribund	No	1/10/94	VV	68	Yes
49	36	M	Viral pneumonia (varicella zoster)	Pneumonia (v)	ARDS	53	4	Moribund	No	2/3/94	VV	214	Yes
50	33	F	Collagen vascular disease	ARDS	Vasculitis	53	4	>12	No	2/5/94	VV	323	No
51	47	M	Aspiration pneumonia, status post myocardial infarction	Aspiration	ARDS	42	2	Moribund	No	2/10/94	VA → VV	313	Yes
52	18	M	Sickle cell disease, viral pneumonia	Pneumonia (v)	ARDS	84	1	Moribund	Yes	2/11/94	VA → VV	113	Yes
53	34	F	Postoperative adult respiratory distress syndrome, sepsis, necrotizing pancreatitis, status post partial pancreatectomy, cholecystectomy	ARDS	Pancreatitis	46	8	>12	No	3/4/94	VV	696	No
54	19	M	Multiple fractures status post motor vehicle accident, pulmonary contusion, sepsis, bacterial pneumonia	ARDS	Trauma	50	4	Moribunf	No	3/16/94	VV	115	Yes
55	51	F	Bacterial (pneumococcal pneumonia, sepsis	Pneumonia (b)	ARDS	61	3	>12	No	4/7/94	VV	121	Yes
56	28	F	Drug overdose; charcoal aspiration	Airway support	Aspiration	480	1	Moribund	No	4/10/94	VV	71	Yes
57	19	F	Bacterial (pneumococcal) pneumonia	Pneumonia (b)	ARDS	54	3	Moribund	No	5/9/94	VV → VA VV	557	No
58	34	F	Bronchiolitis obliterans with organizing pneumonia (BOOP), gram negative pneumonia	ARDS	BOOP	43	1.5	Moribund	No	5/22/94	VV → VA → VV	576	No
59	26	F	Viral pneumonia	Pneumonia (v)	ARDS	34	1	Moribund	No	5/29/94	VV	281	No

(*continues*)

Appendix 1 (*continued*).

Patient Number	Age (yr)	Sex	Diagnoses	Respiratory Classification	Other Classification	P/F Ratio	Pre-ECLS Ventilator Days	Respiratory Management (hr)	Transport	On ECLS (date)	Mode of ECLS	Duration of ECLS (hr)	Survived
60	36	M	Bacterial (legionella) pneumonia	Pneumonia (b)	ARDS	79	5	Moribund	No	6/22/94	VV	257	Yes
61	48	M	Protozoal (pneumocystis) pneumonia, chronic renal failure status post renal transplant (rejection)	Pneumonia (p)	Transplant, ARDS	63	2	Moribund	No	6/26/94	VV → VA	365	No
62	57	M	Status post redo coronary artery bypass grafting	ARDS	Postoperative	44	2	Moribund	No	7/4/94	VA	126	No
63	19	M	Status post motor vehicle accident, pulmonary contusion, pneumomediastinum	ARDS	Trauma	63	7	Moribund	No	7/27/94	VV	410	No
64	36	M	Status asthmaticus	Airway support	Asthma	152	5	Moribund	Yes	8/5/94	VV	79	Yes
65	33	F	Status asthmaticus	Airway support	Asthma	209	1	Moribund	Yes	8/8/94	VV	117	Yes
66	23	M	Viral pneumonia, pneumomediastinum	Pneumonia (v)	ARDS	64	4	Moribund	Yes	8/23/94	VV	447	Yes
67	57	M	Bacterial (pneumococcal) pneumonia, sepsis	Pneumonia (b)	ARDS	58.7	7	>12	No	9/25/94	VV	30	No
68	52	M	Bacterial (legionella) pneumonia	Pneumonia (b)	ARDS	40	1	Moribund	No	10/27/94	VV	500	No
69	27	M	Aspiration/pulmonary edema, status post hanging (suicide) attempt	ARDS	Trauma	47	1	Moribund	Yes	11/20/94	VV → VA	20	No
70	55	M	Bacterial (legionella) pneumonia	Pneumonia (b)		48	1	Moribund	No	12/4/94	VV	295	No
71	31	M	Cocaine inhalation (pulmonary hemorrhage)	ARDS	Pulmonary hemorrhage	44	2	Moribund	No	12/8/94	VV	231	No
72	37	F	Viral pneumonia	Pneumonia (v)	ARDS	47	7	Moribund	No	12/10/94	VV → VA	586	No
73	23	F	Viral pneumonia	Pneumonia (v)	ARDS	56	4	Moribund	No	12/31/94	VV	442	No
74	36	F	Viral pneumonia, CMV sepsis, status post renal transplant followed by donor nephrectomy	Pneumonia (v)	Transplant	47	6	Moribund	No	1/22/95	VA	64	No
75	48	F	Bacterial (*H. influenza*) pneumonia, left empyema, sepsis	Pneumonia (b)	ARDS	65	4	>12	No	2/12/95	VV	476	Yes
76	46	F	Status post total abdominal hysterectomy, bilateral salpingoophorectomy (tuboovarian abscess), sepsis	ARDS	Sepsis	81	2	Moribund	Yes	2/15/95	VV	149	Yes
77	22	M	Bacterial pneumonia	Pneumonia (b)	ARDS	75	1	Moribund	Yes	2/25/95	VV	229	Yes
78	33	F	Viral (varicella zoster) pneumonia	Pneumonia (v)	ARDS	61	1	Moribund	No	4/20/95	VV	258	Yes
79	35	F	Systemic lupus erythematosus	ARDS	Vasculitis	57	1	Moribund	Yes	6/11/95	VV	109	Yes
80	26	F	Viral (varicella zoster) pneumonia	Pneumonia (v)	ARDS	54	2	Moribund	No	6/24/95	VV → VA	307	No
81	26	F	Viral (varicella zoster) pneumonia, 17 wk pregnant	Pneumonia (v)	ARDS	63	8	Moribund	Yes	6/29/95	VA → VA → VV	1357	No
82	34	F	Bronchiolotis obliterans (BOOP)	ARDS	BOOP	53	2	Moribund	No	7/5/95	VV	654	Yes
83	19	M	Status post motor vehicle accident, pulmonary contusions, multiple fractures	ARDS	Trauma	128	1	Moribund	Yes	7/29/95	VV	81	Yes
84	32	F	Bacterial (streptococcal) pneumonia	Pneumonia (b)	ARDS	42	1	Moribund	Yes	10/10.95	VV	863	No

(*continues*)

Appendix 1 (*continued*).

Patient Number	Age (yr)	Sex	Diagnoses	Respiratory Classification	Other Classification	P/F Ratio	Pre-ECLS Ventilator Days	Respiratory Management (hr)	Transport	On ECLS (date)	Mode of ECLS	Duration of ECLS (hr)	Survived
85	25	M	Status post motor vehicle accident, bilateral lower extremity fractures	ARDS	Trauma	64	5	Moribund	Yes	10/22/95	VA	438	No
86	23	F	Bacterial (streptococcal) pneumonia, purpura fulminans, consumptive coagulopathy, history of thrombotic thrombocytopenic purpura, status post splenectomy, sepsis	Pneumonia (b)	ARDS	40	2	>12	No	12/7/95	VV	274	Yes
87	49	M	Lung transplant rejection, status post left orthotopic lung transplant, underlying α_1-antitrypsin deficiency	ARDS	Transplant	61	3	>12	No	12/23/95	VV	113	Yes
88	33	F	Bacterial (streptococcal) pneumonia	Pneumonia (b)	ARDS	66	2	Moribund	Yes	12/26/95	VV	69	Yes
89	43	F	Status asthmaticus	Airway support	Asthma	291	3	Moribund	No	1/26/96	VV	14	No
90	44	M	Urosepsis, consumptive coagulopathy	ARDS	Sepsis	50	1	Moribund	Yes	2/7/96	VV	117	No
91	47	M	Bacterial (streptococcal) pneumonia, sepsis	Pneumonia (b)	ARDS	55	4	Moribund	Yes	2/7/96	VV	117	No
92	40	M	ARDS status post thoracoabdominal aortic aneurysm repair	ARDS	Postoperative	93	3	Moribund	No	2/18/96	VV	109	Yes
93	63	M	Subacute rejection (14 days) status post right orthotopic lung transplant complicated by bronchopleural fistula	ARDS	Transplant	93	3	Moribund	No	2/25/96	VV	142	No
94	25	M	Bacterial (streptococcal) pneumonia	Pneumonia (b)	ARDS	45	0.5	Moribund	Yes	5/1/96	VV	406	Yes
95	39	F	Toxic shock syndrome (gram positive cocci), status post left modified radical mastectomy	ARDS	Sepsis	41	0.5	Moribund	No	5/29/96	VA	120	Yes
96	22	F	Chemical pneumonitis	ARDS	Sepsis	58	0.5	Moribund	Yes	6/4/96	VV	165	Yes
97	19	M	ARDS	ARDS	Unknown	46	1	Moribund	Yes	6/20/96	VV	279	Yes
98	40	F	Reperfusion injury status post orthotopic lung transplant, underlying α_1-antitrypsin deficiency	ARDS	Transplant	40	0.5	Moribund	No	7/2/96	VV	56	Yes
99	19	F	ARDS	ARDS	Unknown	78	7	>12	No	7/2/96	VV	247	No
100	60	F	Viral pneumonia	Pneumonia (v)	ARDS	70	3	Moribund	Yes	7/26/96	VV	127	No
101	19	M	Viral pneumonia, viral cardiomyopathy	Pneumonia (v)	ARDS	58	3	Moribund	Yes	7/29/96	VA → VV	138	Yes
102	28	F	Necrotizing pancreatitis, status post pancreatic debridement	ARDS	Pancreatitis	67	7	Moribund	No	8/9/96	VV	177	Yes
103	60	M	Bacterial (legionella) pneumonia	Pneumonia (b)	ARDS	61	2	Moribund	No	8/9/96	VV	162	Yes

ARDS = adult respiratory distress syndrome; ECLS = extracorporeal life support; CABG = coronary artery bypass graft; BOOP = bronchiolitis obliterans organizing pneumonia; VV = venovenous; VA = venoarterial; Pneumonia (b) = Pneumonia (bacterial); Pneumonia (v) = Pneumonia (viral); Pneumonia (p) = Pneumonia (protozoan).

* Represents pilot study patients and not included in the report of 100 adult extracorporeal life support patients. P/F ratio, p_aO_2/F_iO_2 ratio; VV, venovenous; VA, venoarterial. Moribund, refers to patients who experienced immediate profound cardiorespiratory deterioration despite any intervention and underwent immediate institution of extracorporeal life support (see text); >12 hours, refers to patients who underwent our treatment of optimal therapy for greater than 12 hours yet required extracorporeal life support (see text).

Discussion

DR. ALDEN H. HARKEN (Denver, Colorado): I must say I think this is an extraordinarily important topic, and I would commend Dr. Kolla for a nice presentation and Dr. Bartlett for extending his previous work. I would be remiss if I didn't point out that on my first day as a surgical intern I had the good fortune of meeting Dr. Bartlett as my senior resident. He has been educating me about surgery and surgical critical care ever since.

With Dr. Bartlett's leadership now more than 10,000 newborns have been treated with extracorporeal membrane oxygenation (ECMO) or extracorporeal lung support and with a greater than 80% survival in what was previously a lethal disease. And Dr. Bartlett has really led the way in extending ECMO into the adult realm. But advancing age has always been an ominous risk factor. And I don't need to tell the membership of this Society that old age is not for sissies. I have five brief questions.

The first is, Dr. Bartlett, you were presented 141 patients who other critical care surgeon physicians apparently thought were very sick. Only two thirds of those did you think were sick enough for this kind of extraordinary ECMO support. My sense is that group must have been incredibly sick. Do you have any sense for what the outcome would have been in a control population that didn't have your kind of support? Second, you know hearts and lungs are reasonably simple organs, their purpose being to deliver oxygen. One of the easy ways to increase oxygen delivery is to transfuse the patient. A National Institutes of Health (NIH) Consensus Conference has, in their infinite wisdom, told us that anybody with a hematocrit more than 21 doesn't need to be transfused. What is your transfusion trigger? Third, Dr. Shoemaker has presented some very interesting data suggesting that if we deliver oxygen at supranormal levels in critically ill patients we get better outcomes. You have got an opportunity with ECMO to control, especially with venoarterial access, oxygen delivery in a way you usually can't. What is the purpose of pushing oxygen delivery up into the flow-independent levels? Fourth, there are some obvious disadvantages to an artificial surface–blood interface. I think of neutrophils and platelets, seeing that artificial surface and expressing β integrins, priming themselves for protease and oxidant release. Have you looked at formed blood elements relative to their primed status? Finally, if you place a patient on a ventilator for a while, I think if they are not able to get rid of their secretions very well, they exhibit a kind of a smoldering inflammation.

One of the problems in these kinds of protracted lung problems is the obligate—I think of it as being obligate—pulmonary fibrosis. What can we do about changing this inflammatory process into fibrosis? Can we prevent that?

DR. GRAEME L. HAMMOND (New Haven, Connecticut): This is a superb series, and addresses a serious problem. I would like to ask a question about one group of your patients, those with adult respiratory distress syndrome (ARDS).

We have been treating those patients at Yale, when they are referred to us, with the intra-aortic balloon. This allows us to maintain satisfactory cardiac output at much lower filling pressures. The patients can then be given diuretics to the point that pulmonary interstitial fluid moves back into the vascular space by Starling forces. We have been able to rescue patients with this technique on the average of 24 to 48 hours of balloon pumping and then are able to take the balloon out. I wondered if your group has had any experience with this approach?

DR. FRANK R. LEWIS (Detroit, Michigan): I certainly extend my compliments to Dr. Bartlett and his coworkers for an extraordinary piece of work and for reactivating interest in adult extracorporeal membrane oxygenation (ECMO). I have three questions.

First, as I interpreted your results, the patients who were referred for ECMO but whom you did not put on ECMO because you demonstrated some improvement appeared to have a survival rate of about 65% or 70%. Your criterion in that group for ECMO *versus* no ECMO was improvement during the first several hours at your institution. Could you tell us what improvement consisted of, what the criteria were for describing that, because that survival rate, if I interpreted it correctly, is comparable to your other group. The question is, in that group or in a comparable control group, how would they have done?

Second, to extend Dr. Harken's question, if you transfused patients to achieve a normal hematocrit you should be able to bring their cardiac output down significantly, which in turn would reduce the pulmonary artery hydrostatic pressure and reduce the tendency for edema formation. Have you had a protocol for doing that? Do you have a minimum hemoglobin that you keep these people at? And what do you think the effects of that are?

Third, you indicated that the great majority of these patients who survived are pursuing normal activities after recovery. Years ago when we followed a number of patients who had been on a ventilator for more than 2 months and survived, and we studied them long-term, we found that they had significant loss of diffusing capacity and long-term restriction of their lung compliance. Although they were able to pursue normal daily activities, they could not exercise at maximal rates for their age and condition, and they did have significant impairment of their pulmonary function under stress. Have you studied these patients in a similar way?

DR. CAROL E. H. SCOTT-CONNER (Iowa City, Iowa): We have followed with great admiration the work of Dr. Bartlett's group in the treatment of patients with severe respiratory failure. I have just one question to ask the group, and that is, what are the problems that remain to be surmounted both technologically with the device itself and medically with the management of these patients? This is a superb series and wonderful results. I can't help thinking that perhaps if the modality were a little bit easier to administer or a little bit less prone to complications we might be able to use it for more of these critically ill patients. So I would like to know their perspective on what remains to be done to make this easier to use.

DR. FRANK C. SPENCER (New York, New York): How many in the audience have an extracorporeal membrane oxygenation (ECMO) program in your own institution? Raise your hands, please. (A large number of hands were raised.) It is evident that ECMO is widely used, speaking for its importance. The exact benefit, however, is difficult to measure.

It is similar to the difficulty with measuring the benefit from

an intra-aortic balloon pump. If ECMO is started early, with good-risk patients, the results are very good, but one is probably treating a lot of people who didn't need it. On the other hand, if ECMO is begun too late with a fixed irreversible pulmonary injury, there is very high mortality; so the ECMO cannot be demonstrated to be of much benefit.

I have two questions. First, what are your current indications and contraindications?

Second, what is the level of anticoagulation you used. I noticed that two of the deaths reported were from intracranial bleeding. Thank you for an important contribution.

DR. ROBERT H. BARTLETT (Closing Discussion): Thank you very much to the discussants for their kind comments and their very perceptive questions. Because most of these patients were placed on extracorporeal life support emergently, (75 of them, and half of those in referral hospitals), there really is no comparable group in the literature. These are patients who are in the acute stage of dying from acute respiratory failure.

The survival in our patients managed selectively by the protocol that we discussed was 66% compared with 40% in a prospective randomized trial of extracorporeal CO_2 removal (an extracorporeal membrane oxygenation [ECMO] variant) by Dr. Allen Morris in Salt Lake City (Am J Respir Crit Care Med 1994;149:295). One of the impressive parts about Dr. Morris's study was a 42% survival in the control group with conventional therapy.

As Dr. Lewis pointed out, our comparable non-ECLS group actually did very well. About 80% of those patients survived. The deaths in this group were related to brain injury and other things. So we can at least compare with the Morris study, which is a very tightly controlled protocol for ventilator management.

Perhaps more representative is the paper by Dr. Vasilyev (Chest 1995;107:1083) representing 25 major centers documenting experience with very severe respiratory failure in the year 1992. Twenty percent of patients who are classified similarly to our patients ultimately survived. There is definitely a need for a prospective study of this protocol (for which we have claimed such good results) compared with other approaches to management with or without extracorporeal support.

With regard to transfusion and systemic oxygen delivery, we manage these patients with a normal hematocrit. I have to keep reminding our residents that the normal hematocrit is 48% and the normal hemoglobin is 15 g/dL. We all have developed the habit of managing patients with controlled anemia in our intensive care units (ICUs). There is nothing wrong with that; it is certainly good to avoid transfusion if we don't need it. However, the problem in patients who have severe respiratory failure is systemic oxygen delivery and getting oxygen from the lung into the blood. One of the ways to optimize that is simply by making their hematocrits normal. It is particularly important in the extracorporeal support patients because the limiting factor is the amount of blood flow that can run through the machinery. Each milliliter of blood that goes through needs to have a lot of hemoglobin in it to fully oxygenate the patient when oxygenation is an issue.

As Dr. Harken points out, the concept of what has been called supranormal delivery is a fascinating one worthy of a lot of study and discussion. We maintain oxygen delivery in the range of four to five times oxygen consumption, which in fact is the normal ratio in a healthy person. That translates to a venous blood saturation of 75% to 80%, and that is exactly what we strive for. If the metabolic rate is increased because of sepsis or inflammation, then the oxygen delivery will be increased in proportion. But we don't consider that supranormal, we consider that just normal adaptation to hypermetabolism. We do think it is important to focus on systemic oxygen delivery and we have the ability in these patients to control it quite easily.

Pulmonary fibrosis, as Dr. Harken mentioned, is certainly a problem. It is the cause of death in most of our patients. We are in the midst of studies to focus on the fibroblast and collagen formation to determine how to prevent that process in the healing of lung injury.

Several of the discussants asked indirectly about blood surface interaction and what happens to the anticoagulation. Dr. Spencer, we do manage with continuous heparin anticoagulation these patients. We keep the activating clotting time at a slightly elevated level, 160 to 180 seconds. Nonetheless, bleeding is a problem that is related to blood surface interaction between platelets and the plastic surfaces. Recent work in our laboratory shows considerable progress in avoiding that problem. Unfortunately, heparin coating of the surfaces has not solved the problem because heparin coating doesn't address the platelet–surface interaction.

Dr. Hammond's approach with maximizing delivery by balloon pumping is fascinating. We have no experience with it.

And, Dr. Lewis, on detailed testing there is a slight to moderate reduction in total lung volumes and perhaps a slight reduction of diffusion capacity. However, our patients have not experienced significant exercise limitation.

Reprinted from ASAIO JOURNAL, September-October, 1997
Published by Lippincott-Raven Publishers
Vol. 43, No. 5 Printed in U.S.A.

Total Respiratory Support With Tidal Flow Extracorporeal Circulation in Adult Sheep

*SRINIVAS KOLLA, *STEFANIA CROTTI, *W. ANTHONY LEE, *MATTHEW J. GARGULINSKI, †THOMAS LEWANDOWSKI, †DAVID BACH, *RONALD B. HIRSCHL, AND *ROBERT H. BARTLETT

A novel pressure gated tidal flow extracorporeal circulation (TF ECC) device was developed, and it was hypothesized that it could provide total respiratory support in apneic adult sheep without adverse hemodynamic or cardiac effects. The circuit consisted of a single lumen cannula, computer driven tubing occluders gated by circuit pressure, a nonocclusive peristaltic blood pump, a spiral coiled membrane lung, and a heat exchanger. Six paralyzed, anesthetized adult sheep were instrumented and TF ECC was instituted via cannulation of the right atrium. Total respiratory support was provided by the circuit during an apneic period of 6 hours. Echocardiography was performed with the animal instrumented (baseline) and after 2 hours of TF ECC. Circuit blood tidal volume was 172.6 ± 18.0 cc, resulting in a TF ECC flow of 71.1 ± 10.1 cc/kg/min. At the end of the study period, P_aCo_2 was 35.5 ± 7.6 mmHg, p_aO_2) was 91.2 ± 30.6 mmHg, and pulmonary artery oxygen saturation ($S_{PA}O_2$) was 95 ± 5%. Hemodynamic stability was maintained with no significant differences at baseline and after 6 hours in mean arterial pressure, mean pulmonary artery pressure, or heart rate noted. Echocardiographic evaluation showed preserved fractional shortening of the left ventricular (LV) septal–lateral dimension (baseline 32.4 ± 11.4 %; 2 hours 34.8 ± 8.4 %). This study demonstrates TF ECC provides total respiratory support without adverse hemodynamic effects, and preserved LV function. *ASAIO Journal* 1997; 43:M811–M816.

Continuous flow veno-venous (VV) extracorporeal life support (ECLS) has been successful in treatment of adults and children with severe respiratory failure.[1,2] The drawbacks of this technique are: 1) it requires a double lumen catheter or two operative sites for placement of cannulae, 2) it incurs the potential morbidity of femoral vein occlusion when that site is used, 3) it allows recirculation of circuit flow that restricts the amount of oxygen transfer, and 4) it is cumbersome and requires the constant presence of an ECMO specialist to monitor the circuit. Tidal flow extracorporeal circulation, on the other hand, minimizes or eliminates these problems.

The concept of tidal flow was introduced by Kolobow *et al.* at the National Institutes of Health in 1982 and used in small sheep with experimental respiratory failure.[3–6] Chevalier *et al.* demonstrated the use of a tidal flow circuit in neonates and small children and showed its clinical efficacy, ease of applica-

From the Departments of *Surgery and †Cardiology, University of Michigan Medical Center, Ann Arbor, Michigan.

Presented at the 43rd Annual Meeting of the American Society of Artificial and Internal Organs, May 1–3, 1997, Atlanta, Georgia

Reprint requests: Robert H. Bartlett, MD, University of Michigan Medical Center, 1500 E. Medical Center Drive, 2918 Taubman Center, Box 0331, Ann Arbor, MI 48109-0331.

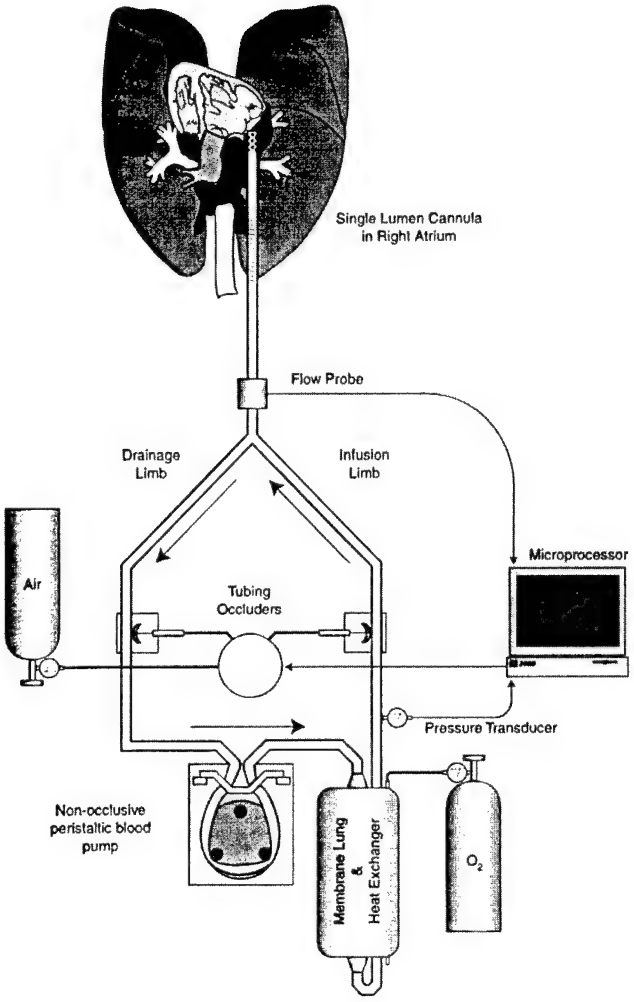

Figure 1. Schematic of the tidal flow extracorporeal circulation device.

tion, and requirement for minimal attendance.[7] Both of these systems, however, used small blood tidal volumes, generated relatively low bypass flows, and were used primarily for extracorporeal CO_2 removal ($ECCO_2R$), combined with oxygenation via apneic lungs. The application of tidal flow extracorporeal circulation to larger patients or animals, or for total respiratory support, presents problems in bioengineering addressed in this study.

Methods

Device Description

The device (**Figure 1**) consisted of a single lumen cannula (25 Fr, Biomedicus, Eden Prairie, MN) connected to both the drainage (1/2-inch Tygon, Norton Plastics, Akron, OH) and infusion (3/8-inch Tygon) limbs. The drainage and infusion limbs were connected to a peristaltic pump (M-pump). A detailed description of this pump has been reported,[8] and is only briefly restated here. The pump consists of a distensible ribbon-like pump chamber and is nonocclusive, which allows minimal hemolysis. Further, it has inherent pressure regulation, and is flow dependent on available supply. A solid, silicone, spirally wound membrane lung with an integral heat exchanger (4.5 m^2, Avecor Cardiovascular, Plymouth MN) was used for gas exchange and temperature regulation. Pneumatically driven (50 psi) tubing occluders, actuated by solenoids, were applied to both the drainage and infusion limbs. A pressure transducer, placed after the membrane lung (but before the infusion tubing occluder) in the infusion limb of the circuit provided continuous circuit pressure signals. An ultrasonic flow probe (Transonic Systems Inc, Ithaca, NY) was placed around the cannula and provided continuous flow signals.

A computer (Apple Macintosh, Cupertino, CA) continuously monitored circuit pressures and triggered the tubing occluders to alternate clamping of the drainage and infusion limbs, thereby effecting tidal flow based on these pressures. In addition, the computer determined infusion and drainage times, performed integration of the infusion flow signal (minus dead space of cannula) to determine infusion blood volume measurements and, from these, determined circuit flow per cycle (blood tidal volume/cycle time). The averages of these parameters over 30 cycles were also monitored.

Circuit Controller

The operation of the circuit works with pressure gating the alternating tubing occluders (**Figure 2**). Initially, when the circuit pressure is low, the drainage occluder is open and the infusion occluder is closed. Drainage occurs passively with gravity and fills the infusion side of the pump chamber. The pump displaces this volume into the infusion limb—the outflow side of the pump chamber and the membrane lung. The volume displaced in this fashion is a function of the compliance of the infusion limb (mostly composed of the compliance of the membrane lung). When the circuit pressure then exceeds a preset high pressure limit during the drainage phase, the infusion occluder opens while the drainage occluder closes. Infusion proceeds until a preset low pressure limit is met, at which point the clamps reverse and the cycle begins anew.

Circuit Priming

Priming of the circuit involves the addition of 1–2 L lactated Ringer's solution while exposing the gas phase of the membrane lung to vacuum (−100 cm H_2O) and circulating the solution for approximately 30 min until air bubbles were no longer visibly detected. The crystalloid prime was then replaced with 1–2 U whole blood to which 1000 u heparin

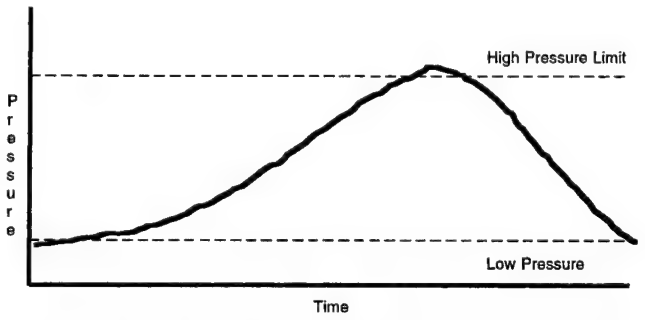

Figure 2. Circuit pressure for a single cycle illustrating pressure-gated control of TF ECC.

were added. Blood chemistries were measured using the GEM Premier Blood Gas and Electrolyte Analyzer (Mallinckrodt, Ann Arbor, MI), and whole blood activated clotting time (ACT) was measured with the Hemochron 401 Blood Coagulation Timing System (ITC Corp., Edison, NJ). Calcium chloride, sodium bicarbonate, and additional heparin were added as needed to keep electrolytes and pH within the normal range and ACT at 300–400 sec. Carbogen (5%) gas was administered as the ventilating gas to maintain p_aCO_2 in the normal range. This ventilating gas was changed to 100% oxygen as soon as TF ECC was initiated.

Experimental Conduct

Six adult sheep were administered intravenous sodium pentobarbital (20 mg/kg) to induce anesthesia. The animals were then instrumented with a tracheostomy and connected to a mechanical ventilator with settings to maintain normal arterial blood gases. A femoral arterial line, and a femoral venous catheter (9 Fr), were then placed. A maintenance intravenous saline solution was given (0.9 NS, 10 cc/kg/hr). After the administration of an intravenous heparin bolus (300 U/kg), a cannula was introduced into the right atrium via cut-down of the right internal jugular vein. An Oximetrix® pulmonary artery catheter (Oximetrix Inc, Mountain View, CA) was then advanced via the femoral catheter into the pulmonary artery. Baseline measurements after instrumentation were obtained. The cannula was connected to the circuit and TF ECC was gradually introduced over a 5–10 min period by slowly increasing circuit settings and monitoring pulmonary artery saturation. Immediately after the institution of full TF ECC support, the endotracheal tube was clamped and the animal disconnected from the ventilator. There was no requirement for pressors or additional intravenous fluids. Ultimately, the high pressure limit was set at 425 mmHg, while the low pressure limit was set at 125 mmHg. The pump speed was maintained between 60–90 rpm. Ventilating gas rates were maintained at 1–4 L/min and adjusted as needed for carbon dioxide clearance.

The animals were maintained on TF ECC for total respiratory support during the 6-hour study period. Whole blood activated clotting times were monitored hourly (Hemochron 401) throughout the experiment and maintained at 300–400 sec through the intravenous administration of additional heparin. Supplemental doses of sodium pentobarbital were administered as needed for anesthesia throughout the study period. At the end of the experiment, the animals were killed with the administration of 10 cc of Beuthanasia-D (Schering-Plough, Kenilworth, NJ).

Echocardiography

Transthoracic echocardiography (Acuson Corp, Mountain View, CA) was performed on all animals. Biplane images of the left ventricular (LV) cavity in both short and long axis views, as well as M-mode images of the midventricular LV septal–lateral (SL) cavitary dimension, were obtained. Two-dimensional guided M-mode images were used to derive data to assess changes in the LV SL dimension during drainage and infusion phases of TF ECC, and to estimate fractional shortening of this dimension. The LV SL dimension was measured between the endocardial borders of the ventricular septum and the LV free wall. The LV SL fractional shortening was determined as the percent change in this dimension from diastole to systole.[9] Average values of LV SL fractional shortening were obtained for each animal from three representative beats during diastole and systole. Percent change in LV SL dimension between drainage and infusion was determined by assessing this dimension during the drainage and infusion phases of TF ECC. Average values of this dimension were obtained for each animal from three representative beats during drainage and infusion. Valvular function was assessed using Doppler echocardiography. Valvular regurgitation was graded on a scale of absent, mild, moderate, and severe.[10] Trace regurgitation was noted but was considered physiologically normal.

Measurement of Oxygen and Carbon Dioxide Transfer

Oxygen (VO_2) and carbon dioxide (VCO_2) transfer across the membrane lung during tidal flow were measured with an indirect, calorimetric technique using a device previously described and validated by this laboratory.[11,12] Briefly, the device consists of an occlusive roller pump (Cobe Cardiovascular, Inc. Arvada, CO) that induces gas flow at a prescribed rate through a closed circuit consisting of a 9 L spirometer (Warren E. Collins, Inc., Braintree, MA), a mixing chamber, a capnometer (Rascal II, Ohmeda, Salt Lake City, UT), and a CO_2 scrubber (Dryden Co., Indianapolis, IN). This device was configured to ventilate the membrane lung, thereby allowing measurement of gases across the membrane lung. The VO_2 was evaluated by measurement of volume loss from the spirometer in the closed circuit. Because carbon dioxide is deleted from the circuit by the CO_2 scrubber, volume loss in the leak free circuit is only secondary to oxygen consumption. The VCO_2 was analyzed through a capnographic assay of the mixed expired closed circuit air. The VCO_2/VO_2 ratio (RQ) was calculated as well.

Data Collection

Mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), and heart rate (HR) were monitored continuously and recorded hourly. The saturation of pulmonary arterial blood ($S_{PA}O_2$) was monitored continuously with the Oximetrix pulmonary artery catheter. Arterial blood gases were assessed using the GEM Premier Blood Gas Analyzer (Mallinckrodt, Ann Arbor, MI), and arterial oxygen saturation data were evaluated using an OSM 3 co-oximeter (Radiometer A/S, Copenhagen, Denmark). These data were obtained hourly. Echocardiography was performed at baseline and after 2 hours of TF ECC. Measurements of oxygen and carbon dioxide transfer across the membrane lung were obtained after 3 hours of TF ECC. All data were recorded as mean ± standard deviation. Statistical comparisons were made with Student's t-test.

This study was performed under protocols approved and reviewed by the University Committee on the Use and Care of Animals at the University of Michigan Medical Center and guidelines set forth by the National Institutes of Health.

Results

Six adult sheep, 29.2 ± 3.2 kg, were supported with tidal flow extracorporeal circulation for the extent of the study period. The average circuit settings at total respiratory support

Table 1. Tidal Flow Extracorporeal Circulation Circuit Parameters, Arterial Blood Gases, and Hemodynamic Parameters

Circuit parameters	
V_t (cc)	172.6 ± 18.0
Flow (L/min)	2.1 ± 0.2
T_i (sec)	2.19 ± 0.29
T_d (sec)	2.92 ± 0.62
Cycles (Hz)	12.2 ± 1.7
RPM	73.3 ± 4.6
Flow/weight (ml/kg/min)	71.1 ± 10.1
Arterial blood gases and hemodynamics	
pH	7.49 ± 0.05
pa_{CO_2} (mmHg)	35.5 ± 7.6
pa_{O_2} (mmHg)	91.2 ± 30.6
Sa_{O_2} (%)	95.7 ± 4.0
SPA_{O_2} (%)	95 ± 4
MAP (mmHg)	106.7 ± 12.6
MPAP (mmHg)	30.0 ± 9.8
HR (bpm)	117.8 ± 4.8

TF, ECC, V_t, blood tidal volume; T_i, infusion time; T_d, drainage time; RPM, revolutions per minute; P_aCO_2, arterial carbon dioxide tension; P_aO_2, arterial oxygen tension; S_aO_2, arterial oxygen saturation; $S_{pa}O_2$, pulmonary arterial oxygen saturation; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; HR, heart rate.

levels are shown in **Table 1.** The average drainage and infusion times, a function of the pressure characteristic of the circuit, were 2.92 ± 0.62 sec and 2.19 ± 0.29 sec, respectively. The average calculated blood tidal volume, a function of the infusion limb circuit compliance, was 172.6 ± 18.0 cc. Average cycling frequency was 12.2 ± 1.7/min, resulting in a TF ECC flow of 2.1 ± 0.2 L/min (71.1 ± 10.1 cc/kg/min).

Arterial Blood Gases and Hemodynamics

Arterial blood gas measurements and hemodynamics after 6 hours of TF ECC are shown in **Table 1.** The average blood gases are within normal limits and indicate adequate oxygenation and ventilation. The $S_{PA}O_2$ is a direct measurement of the saturation of arterialized blood in the pulmonary artery delivered by the circuit, and the average $S_{PA}O_2$ of 95 ± 5% reflects the ability of the circuit to provide oxygenation support. The arterial saturation S_aO_2 and $S_{PA}O_2$ were nearly equal (96 % *vs.* 95 %, respectively) and not statistically different, which indicates total oxygenation provided by the circuit with no contribution by the native lungs.

Hemodynamics at baseline and after 6 hours show no significant differences in MAP, MPAP, or HR **(Table 2)**. The experimental course of a representative animal is shown in **Figure 3.**

Variations in systemic and pulmonary arterial pressures with tidal flow are demonstrated in **Figure 4.** Interestingly, these variations are 180° out of phase. Therefore, when systemic arterial pressure is at a maximum, pulmonary artery pressure is at its minimum, and vice versa.

Table 2. Comparison of Hemodynamics at Baseline and After 6 Hours of Tidal Flow Extracorporeal Circulation

	Baseline (pre-TF ECC)	6 hr	*p* Value
MAP (mmHg)	105.1 ± 10.1	106.7 ± 12.6	NS
MPAP (mmHg)	28.5 ± 8.5	30.0 ± 9.8	NS
HR (bpm)	118.8 ± 11.8	117.9 ± 4.8	NS

TF, ECC, MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; HR, heart rate; NS, not significant.

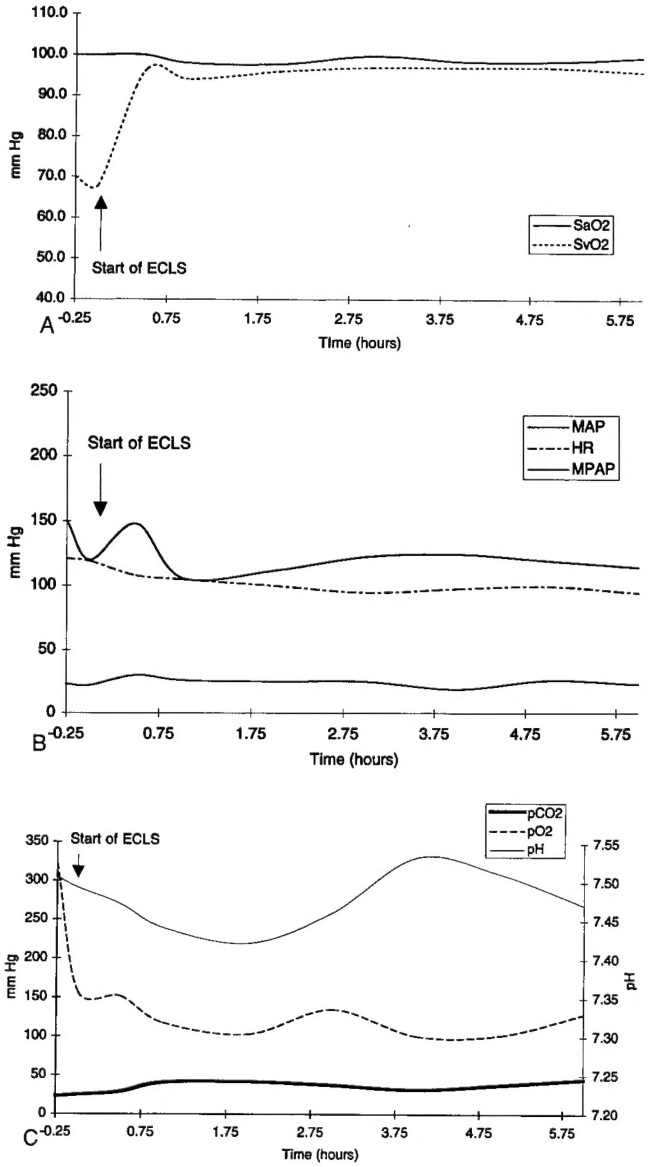

Figure 3. Representative experimental course of an animal during TF ECC. Sheep 4: weight 35.0 kg. The sheep was placed on TF ECC for a period of six hours. The average circuit parameters during the six hours study were: V_T 175.5 cc; Flow 2.0 L/min (57.1 cc/kg/min); T_i 2.04 sec; T_d 2.81 sec; cycles 12.4/min, pressure-gated limits 425/125; RPM 78.3. **A)** Pulmonary Arterial and Systemic Arterial Saturations. Note the increase in $S_{PA}O_2$ with the institution of TF ECC and its equivalency to S_aO_2, indicating total oxygenation. **B)** Hemodynamic Parameters. The hemodynamics and blood gases are stable throughout the period of support. There is a period of relative hypertension during the first hour of TF ECC due to lightening of anesthesia that resolves with the administration of adequate anesthesia. **C)** Arterial Blood Gases. There is a brief rise in pH at approximately the fourth hour of TF ECC corrected by decreasing the ventilating gas and allowing the p_aCO2 to increase from 32 to 45 mmHg. Abbreviations: S_aO_2, arterial saturation; $S_{PA}O_2$; saturation of pulmonary artery blood; MAP, mean arterial pressure; HR, heart rate; MPAP, mean pulmonary artery pressure; p_aCO_2, arterial carbon dioxide tension; p_aO_2, arterial oxygen tension.

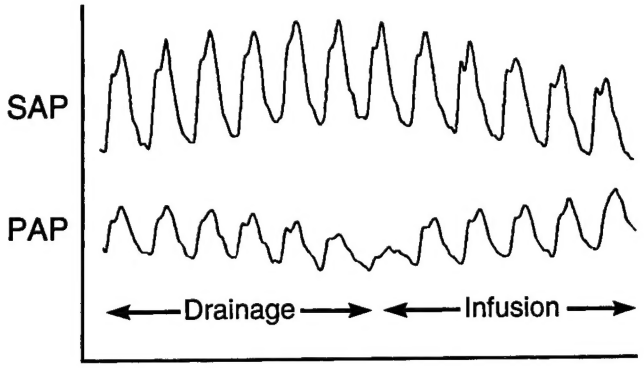

Figure 4. Tidal variation of systemic and pulmonary arterial pressures. SAP, systemic arterial pressure; PAP, pulmonary arterial pressure. Note that systemic arterial pressure increases and pulmonary artery pressure decreases during drainage, while the opposite events occur during infusion.

Echocardiography

All valvular function was within normal limits, except for the tricuspid valve. Tricuspid regurgitation was worse at the end of the infusion phase, and virtually nonexistent during the drainage phase. At baseline, one of the six animals had trace tricuspid regurgitation. After 2 hours of TF ECC, one of the six animals had no regurgitation, three of the six animals had trace regurgitation, and two of the six animals had mild regurgitation, one of which had trace regurgitation at baseline. As expected, tricuspid regurgitation increased with the institution of TF ECC, but it was minimal to mild in severity, was worse at the end of the infusion phase, and appeared to be of no acute hemodynamic consequence. Fractional shortening of the LV septal–lateral dimension showed no significant difference at baseline and after 2 hours of TF ECC, baseline: 32.4 ± 11.4 %, 2 hours: 34.8 ± 8.4 % (p = 0.456). The septal–lateral dimension was measured during infusion and drainage and found to decrease 21.3 ± 7.9 % with infusion as compared with drainage.

Oxygen and carbon dioxide transfer

The average VO_2 and VCO_2 were 118.8 ± 14.8 cc/min and 90.4 ± 9.6 cc/min, respectively (4.0 ± 0.8 cc/kg/min and 3.0 ± 0.6 cc/kg/min, respectively). The respiratory quotient was 0.76 ± 0.4; VO_2 and VCO_2, normalized for blood flow, were 62.1 ± 16.7 cc/L and 47.0 ± 12.4 cc/L, respectively.

Discussion

Continuous flow VV ECLS has been successful in the treatment of children and adults with severe respiratory failure.[1,2] This mode has advantages over venoarterial bypass in that it avoids carotid artery ligation, allows oxygenated blood through the native pulmonary circulation, eliminates the risk of systemic embolization, and has less potential deleterious effects on cardiac function.[13] However, a limitation of continuous VV ECLS is that it allows recirculation of blood flow that restricts the overall transfer of oxygen across the membrane lung. Normal oxygen delivery can be maintained if the hemoglobin concentration is normal and cardiac output is adequate. When total respiratory support is needed, high flow VV extracorporeal support is usually required, with its potential consequences of hemolysis and platelet destruction, and the relative requirement for high cardiac output to maintain delivery of oxygen.

In addition, continuous veno-venous ECLS requires two operative sites, with the potential morbidity of femoral venous obstruction/occlusion. Single cannula, dual lumen access avoids this problem, but is not a practical solution in adults or larger children because of limitation of catheter size. Currently, the largest catheter manufactured is 15 Fr, which makes it useful only in neonates who weigh less than 6.0 kg. In addition, recirculation of extracorporeal flow with dual lumen catheters depends highly on catheter tip position, but almost always significantly compromises potential support.[14]

TF ECC eliminates or minimizes these problems. The concept of single lumen cannula tidal flow extracorporeal support was introduced by Kolobow at the NIH in 1982, and used for extracorporeal support in severe respiratory failure in lambs and small sheep.[3–6] The circuit consisted of an occlusive roller pump with drainage and infusion reservoirs, time-cycled alternating occluding clamps, and a membrane lung. A variation of Kolobow's circuit was recently reported by Kezler *et al.* and used for partial respiratory support in lambs.[15]

In Paris, Durandy introduced the use of a time-cycled tidal flow system that used a nonocclusive peristaltic pump and eliminated the need for drainage and infusion reservoirs.[16] The circuit was later used in neonates by Chevalier *et al.*, who demonstrated that tidal flow was clinically efficacious, was well tolerated, and could be easily applied and used for prolonged support with minimal attendance.[7] All of these groups, however, emphasized low flow extracorporeal support primarily for CO_2 removal, whereas oxygenation was accomplished by the apneic native lungs (so called extracorporeal CO_2 removal, $ECCO_2R$).

We have designed a novel pressure-gated TF ECC that provided total respiratory support in adult sheep without adverse hemodynamic or cardiac effects. The basis for pressure-gated control is to optimize the use of the compliance of the infusion limb of the circuit. By determining the pressure of the infusion limb, optimal use of the compliance of the membrane lung and infusion portion of the pump chamber to generate relatively large blood tidal volume is possible. In addition, components of different compliance can be placed in the infusion limb (e.g. membrane lungs and pump chambers of various sizes, or a separately constructed compliance chamber) based on the need for delivery of oxygen in a given subject.

Recirculation with TF ECC is minimized because drainage and infusion take place in discrete and exclusive phases. The degree of recirculation is determined by the fraction of "dead space" in the circuit to blood tidal volume. The "dead space" in the circuit is primarily determined by the volume of the common channel to which the limbs of the circuit are connected. Minimizing this volume without compromising drainage minimizes the degree of recirculation. Although not needed in this study, the introduction of a pause at the end of the infusion phase before the onset of the next drainage phase could further minimize recirculation.

Although there are minor variations in MAP and MPAP with TF ECC, tidal variation in pulse pressures of both systemic and

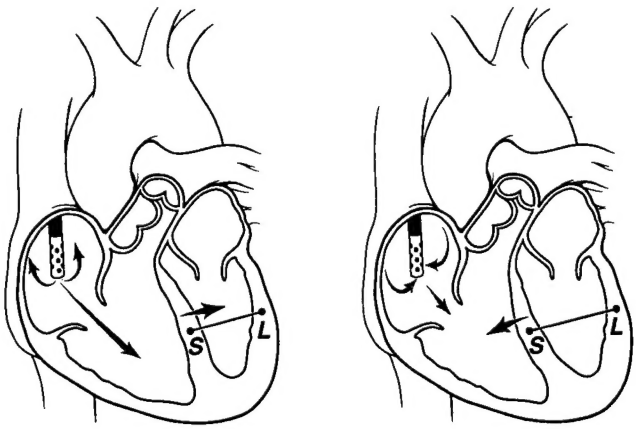

Figure 5. Mechanism of tidal variations in systemic and pulmonary arterial pressures.

pulmonary circulations occurred. The data from our echocardiographic evaluation have allowed us to propose the following mechanism (**Figure 5**). During infusion, a volume of blood (approximately 170 cc) is delivered to the right atrium and, subsequently, to the right ventricle. This causes an increase in right ventricular (RV) cavity size and causes shifting of the septum leftward, which leads to an increase in systolic pulmonary artery (PA) pressure. The LV cavity, on the other hand, decreases in size, as demonstrated by the decrease in the LV SL dimension by 21.3 ± 7.9 % during infusion as compared with drainage, which leads to a smaller LV preload. This results in a decrease in systolic blood pressure (**Figure 4**). During drainage, the opposite events occur. As blood is drained from the right atrium, less blood enters the RV, which causes a decrease in RV preload. This causes a shift of the septum rightward and an increase in LV cavity size and preload, which results in an increase in systolic blood pressure while causing a decrease in systolic PA pressure (**Figure 4**). The pulmonary vasculature undoubtedly plays a role in this phenomenon of ventricular coupling acting as a compliance circuit that mediates changes in RV and LV output.

Average circuit flow in this study was adjusted to support sheep as determined by arterial oxygen saturation greater than or equal to 90%. Attempts to increase flow beyond this level of support were not undertaken. Therefore, the limitation of the device to generate greater flows or support larger animals was not determined in this study. Application of this device to larger animals or patients (e.g., >70 kg) could potentially be accomplished with existing device components. However, further characterization of the device components in terms of circuit compliance (membrane lung and pump chamber size) and cannula size would be necessary to determine the capacity of the device to provide total respiratory support in larger subjects, and is currently ongoing in this laboratory.

Future work with TF ECC includes: 1) characterization of chronic end organ effects, 2) determination of the delivery of oxygen capability of a TF ECC circuit as a function of circuit compliance (membrane lung size and pump chamber size) and cannula size, and 3) clinical application of TF ECC to children and adults with severe respiratory failure.

Conclusions

Tidal flow extracorporeal circulation provides total respiratory support in sheep. Phasic variations in hemodynamics occur, but are well tolerated. Ventricular interdependence, mediated by septal shifting, may be the means by which these variations occur.

Acknowledgments

Study supported in part by a grant from the National Institutes of Health #HD15434.

References

1. Green TP, Timmons OT, Fackler JC, Moler FW, Thompson AE, Sweeney MF: The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. *Crit Care Med* 24:323–329, 1996.
2. Kolla S, Awad S, Rich PB, Schreiner R, Hirschl RB, Bartlett RH: Extracorporeal life support for 100 adult patients with severe respiratory failure. *Ann Surg* (in press), 1997.
3. Kolobow T, Fumagalli R, Arosio P, Chen V, Buckhold DK, Pierce JE: The use of the extracorporeal membrane lung in the successful resuscitation of severely hypoxic and hypercapnic fetal lambs. *Trans ASAIO J* 28:365–368, 1982.
4. Kolobow T, Moretti MP, Mascheroni D, *et al*: Experimental meconium aspiration syndrome in the preterm fetal lamb: successful treatment using the extracorporeal artificial lung. *ASAIO Trans* 29:221–225, 1983.
5. Kolobow T, Borelli M, Spatola R, Tsuno K, Prato P: Single catheter veno-venous membrane lung bypass in the treatment of experimental ARDS. *ASAIO Trans* 34:35–38, 1988.
6. Pesenti A, Kolobow T, Buckhold DK, Pierce JE, Huang H, Chen V: Prevention of hyaline membrane disease in premature lambs by apneic oxygenation and extracorporeal carbon dioxide removal. *Intensive Care Med* 8:11, 1982.
7. Chevalier JY, Couprie C, Larroquet M, Renolleau S, Durandy Y, Costil J: Venovenous single lumen cannula extracorporeal lung support in neonates: a five year experience. *ASAIO J* 39:M654–M658, 1993.
8. Montoya JP, Merz SI, Bartlett RH: Laboratory Experience with a novel, non-occlusive pressure-regulated peristaltic blood pump. *ASAIO J* 38:M406–M411, 1992.
9. Feigenbaum H: *Echocardiography*, 5th ed., Philadelphia, Lea and Febiger, 1994, pp 1–30.
10. Spain MG, Smith MD, Grayburn PA, Harlamert EA, DeMaria AN: Quantitative assessment of mitral regurgitation by Doppler color flow imaging: angiographic and hemodynamic correlations. *J Am Coll Cardiol* 13:585–590, 1989.
11. Cilley RE, Wesley JR, Zwischenberger JB, Toomasian JM, Bartlett RH: Method of pulmonary and membrane lung gas exchange measurement during extracorporeal membrane oxygenation. *ASAIO Trans* 32:525–529, 1986.
12. Hirschl RB, Grover B, McCracken M, Wolfson MR, Shaffer TH, Bartlett RH: Oxygen consumption and carbon dioxide production during liquid ventilation. *J Pediatr Surg* 28:513–518, 1993.
13. Cornish JD, Clark R: Principle and practice of venovenous extracorporeal membrane oxygenation, in Zwischenberger JB, Bartlett RH (eds), *ECMO: extracorporeal cardiopulmonary support in critical care,* Extracorporeal Life Support Organization, Ann Arbor MI, pp 87–109, 1995.
14. Zwischenberger JB, Toomasian JM, Drake K, Andrews AF, Kolobow T, Bartlett RH: Total respiratory support with single cannula venovenous ECMO: double lumen continuous flow vs single lumen tidal flow. *ASAIO Trans* 31:610–615, 1985.
15. Kezler M, Moront MG, Cox C, Milewski M, Visener MS: Oxygen delivery with a single cannula tidal flow venovenous system for extracorporeal membrane oxygenation. *ASAIO J* 41:850–854, 1995.
16. Durandy Y, Chevalier JY, Lecompte Y: Single-cannula venovenous bypass for respiratory membrane lung support. *J Thorac Cardiovasc Surg* 99:404–409, 1990.